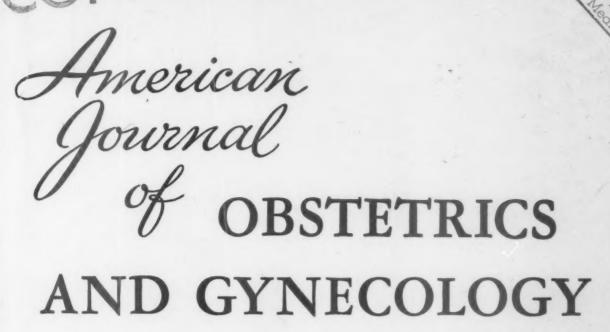
September, 1960 volume 80, number 3



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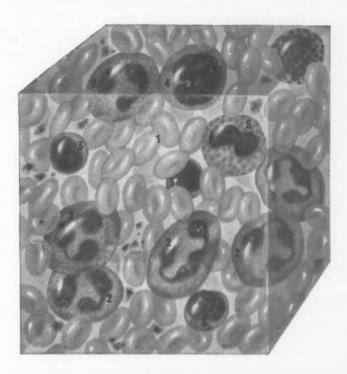
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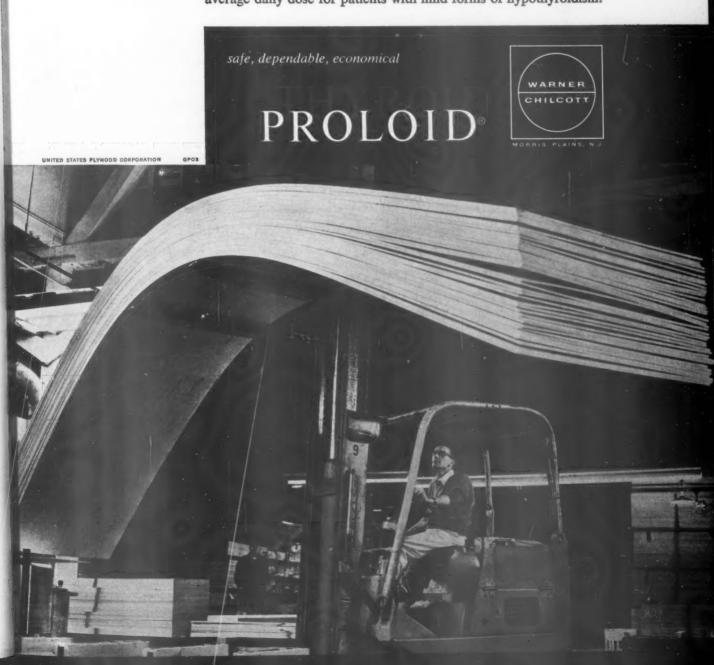
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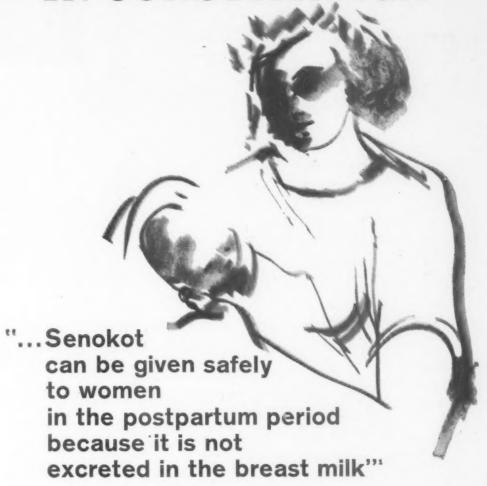
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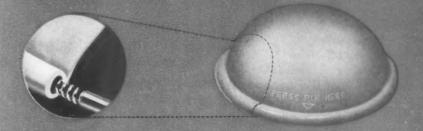
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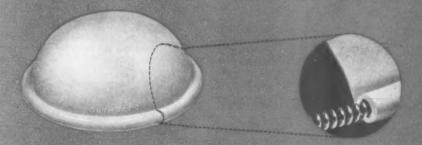
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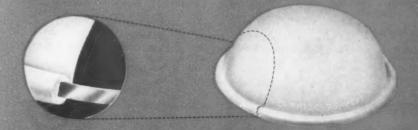
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CARCINOMA IN SITU OF THE UTER-INE CERVIX: A Study of 235 Cases from the Free Hospital for Women by Gilbert H. Friedell, Arthur T. Hertig, and Paul A. Younge, all of Harvard Medical School. A detailed study for those concerned with the diagnosis and management of carcinoma in situ of the uterine cervix. Even in the section devoted to pathology an effort has been made to correlate pathologic with clinical findings. Describes methods for handling biopsy, conization, and hysterectomy specimens in the laboratory for best evaluation of extent of the disease. Pub. date Aug. '60, 164 pp., 98 il. (1 full color plate), \$7.50

TWINS IN HISTORY AND SCIENCE by Luigi Gedda, Instituto Di Genetica Medica, Rome. Although much has been written on the subject of twins, this is the first complete and comprehensive study. Gedda has made use of all available data, including his own personal observations. This book will be of interest to everyone concerned with biological and biopathological problems. It is well-written and excellently illustrated. Pub. date Nov. '60, 292 pp. (7½ x 10), 294 il.

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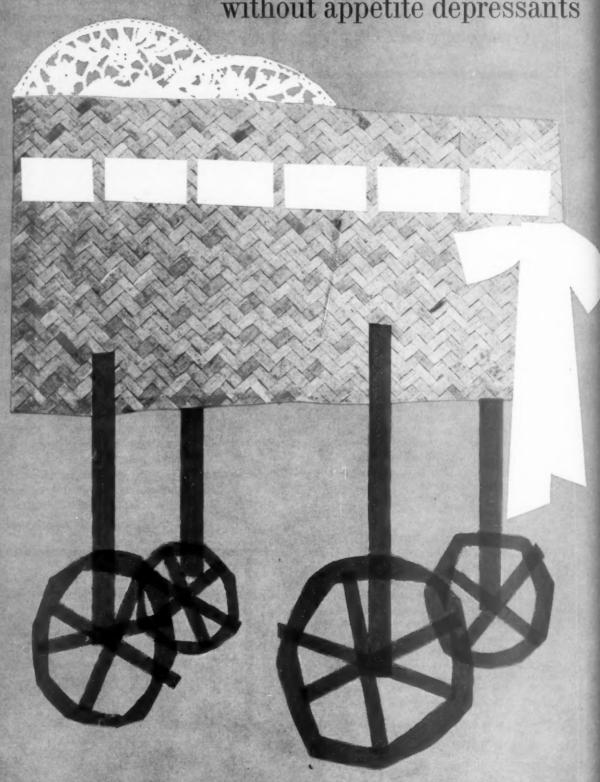
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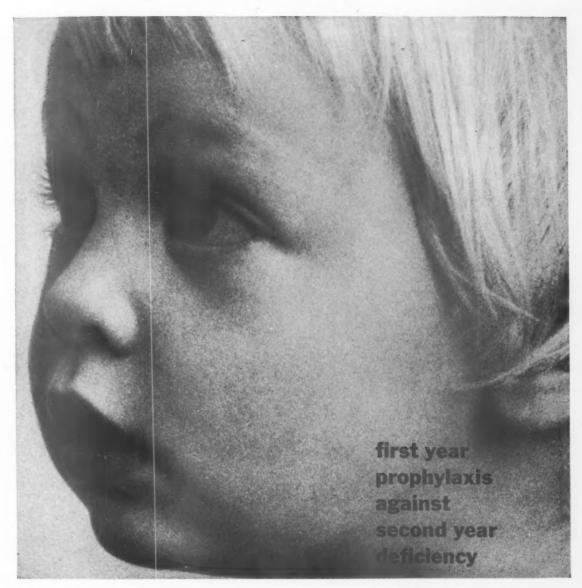
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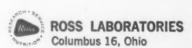
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- · effective in half the dosage required with meprobamate
 - much less drowsiness than with meprobamate, phenothiazines, or the psychosedatives
 - does not impair intellect, skilled performance, or normal behavior
 - neither depression nor significant toxicity has been reported



- · a familiar spectrum of antianxiety and muscle-relaxant activity
- · no new or unusual effects—such as ataxia or excessive weight gain
- · may be used in full therapeutic dosage even in geriatric or debilitated patients
- · no cumulative effect
- · simple, uncomplicated dosage, providing a wide margin of safety for office use

STRIATRAN is indicated in anxiety and tension, occurring alone or in association with a variety of clinical conditions.

Adult Dosage: One tablet three times daily, preferably just before meals. In insomnia due to emotional tension, an additional tablet at bedtime usually affords sufficient relaxation to permit natural sleep.

Supply: 200 mg. tablets, coated pink, bottles of 100.

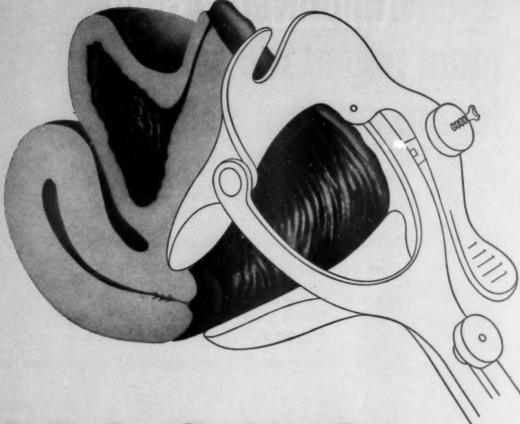
While no absolute contraindications have been found for Striatran in full recommended dosage, the usual precautions and observations for new drugs are advised.

For additional information, write Professional Services, Merck Sharp & Dohme, West Point, Pa.



MERCK SHARP & DOHME, DIVISION OF MERCK & CO., INC., WEST POINT, PA.

STRIATRAN IS A TRADEMARK OF MERCK & CO., INC.



Triple Sulfa Cream

- · in mixed vaginal infections
- against secondary invaders in trichomoniasis
- · in postpartum care
- · after vaginal surgery



Dramatically <u>better</u> management of obstetrical procedures

• AMSCO "800" OBSTETRICAL TABLE

- . . so completely fresh in its design approach as to be truly revolutionary in its convenience and control for operative as well as perineal route delivery.
 - e narrow, flowing lines
 - permanent or portable power base (or new Anesthesia Distribution base)
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AMERICAN STERILIZER

World's largest designer and manufacturer of Sterilizers, Surgical Tables, Lights and related hospital equipment

• Write for these two NEW, fully illustrated brochures:

AMSCO OBSTETRICAL TABLES TC-224-R1
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• AMSCO C-22T5 OBSTETRICAL LIGHT

- ... so advanced in its suspension, positioning and optical system as to establish new standards for obstetrical illumination.
 - absorbs heat-producing infrared rays
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 ever attained
 - travels smoothly, noiselessly over 5-foot extruded aluminum track
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 - dual control of light head . . . by circulating personnel or by obstetrician through patented sterilizable control handle



taken at bedtime

STOPS MORNING SICKNESS IN 94%

OFTEN WITH JUST ONE TABLET DAILY

by treating the symptom nausea and vomiting-as well as a possible specific cause pyridoxine deficiency



Meclizine HCl (25 mg.) for antinauseant action Pyridoxine HCl (50 mg.) for metabolic replacement.

usual dose: One tablet at bedtime; severe cases may require another tablet on arising.

supply: Bottles of 25 and 100 tablets. Bonadoxin also effectively relieves nausea and vomiting associated with: anesthesia, radiation sickness, Meniere's syndrome, labyrinthitis, and motion sickness. Also useful in postoperative nausea and vomiting.

Bibliography on request.

For infant colic, try Bonadoxin Drops. Each cc. contains: Meclizine 8.33 mg.] Pyridoxine 16.67 mg.



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Division, Chas. Pfizer & Co., Inc.
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and ... when your OB patient needs the best in prenatal vitamin-mineral supplementation...

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THE MODERN CHEMICAL SPERMICIDE

THE SPERMICIDAL GEL WITH BUILT-IN BARRIER

PRESCRIBED WITH CONFIDENCE FOR SIMPLE, EFFECTIVE CONTRACEPTION



A brighter "Good morning!"

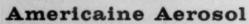
No complaints about

- * post-episiotomy,
- * tender hemorrhoids,
- * or fissured nipples when you prescribe

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Americaine relieves surface discomfort quickly, sustains relief up to six hours with a single application—because only Americaine contains 20% dissolved benzocaine.

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For quick spray application. Available in 3 oz. prescription size, and 5.5 oz. and 11 oz. dispensers.

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1. References on request.

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dual usefulness of



DESITIN

SUPPOSITORIES

with cod liver oil

hemorrhoids pregnancy

0

a suppository, such as **Desitin**, reduces straining at the stool by lubricating the anal canal.¹



conservative treatment is indicated¹⁻³ for mild to moderate symptoms of simple hemorrhoids, fissures, cryptitis, pruritus ani...in pregnant and other patients.

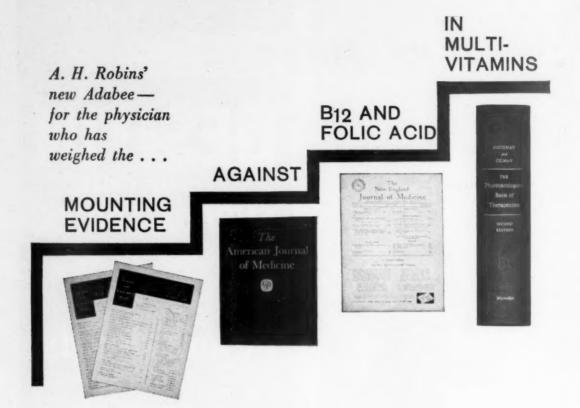
DESITIN SUPPOSITORIES lubricate, soothe, protect, ease pain, itching...and aid healing (with Norwegian cod liver oil, rich in vitamins A and D and unsaturated fatty acids). Free from drugs which might mask serious rectal disease.

Write for samples and literature1-3

DESITIN CHEMICAL COMPANY

812 Branch Ave., Providence 4, R. I.





Individually, folic acid and B₁₂ fill important clinical roles. 1 But, increasing evidence indicates that multivitamins containing folic acid may obscure the diagnosis of pernicious anemia.2-7 And vitamin B₁₂, in indiscriminate and unnecessary usage⁵⁻⁸ is likewise blamed for this diagnostic confusion.7

Both folic acid and B₁₂ have been omitted from Adabee, in recognition of this growing medical concern.

Adabee supplies massive doses of therapeutically practical vitamins for use in both specific and supportive schedules in illness and stress situations. Thus, new Adabee offers the therapeutic advantage of sustained maximum multivitamin support without threat of symptom-masking.

references: 1. Wintrobe, M. M., Clinical Hematology, 3rd ed., Phila., Lea & Febiger, 1952, p. 398. 2. Goodman, L. S. and Gilman, A., The Pharmacological Basis of Therapeutics, 2nd. ed., New York, Macmillan, 1955, p. 1709. 3. New Eng. J.M., Vol. 259, No. 25, Dec. 18, 1958, p. 1231. 4, Frohlich, E. D., New Eng. J.M., 259:1221, 1958. 5. J.A.M.A., 169:41, 1959. 6. J.A.M.A., 173:240, 1960. 7. Coldsmith, G. A., American J.M., 25:680, 1958. 8. Darby, W. J., American J.M., 25:726, 1958.

ADABEE®

Each yellow, capsule-shaped tablet con-

tains:		
Vitamin A		USP units
Vitamin D		USP units
Thiamine mononitrate	(B_1)	15 mg.
Riboflavin (B ₂)		10 mg.
Pyridoxine HC1 (B ₆)		5 mg.
Nicotinamide (niacina)	mide)	50 mg.
Calcium pantothenate		10 mg.
Ascorbic acid (vitamin	(C)	250 mg.

ADABEE® M

Each green, capsule-shaped tablet contains Adabee, plus nine essential minerals:

Iron	15.0	mg.	Zinc 1.5	mg.
Iodine	0.15	mg.	Potassium 5.0	mg.
Copper	1.0	mg.	Calcium 103.0	mg.
Manganese	1.0	mg.	Phosphorus 80.0	mg.
Magnesium	6.0	mg.		0

dosage: One or more tablets a day, as indicated, preferably with meals.

new! Al the multivitamin without B12 or folic acid

A. H. ROBINS COMPANY, INC.

Richmond 20, Virginia



Stops the itch she dreads to scratch

Within minutes, ES-A-CORT can help you control the intolerable discomfort and embarrassment of pruritus vulvae —regardless of cause. Clinical experience has proved ES-A-CORT's balanced combination of hydrocortisone, estrogen, and vitamin A... potentiated by DOME's exclusive ACID MANTLE vehicle... promptly and safely relieves inflammation, itching and edema; facilitates healing, and restores the normal tonicity vitality and protective acidity of mucosa and skin.

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CREME (pH 4.6) LOT

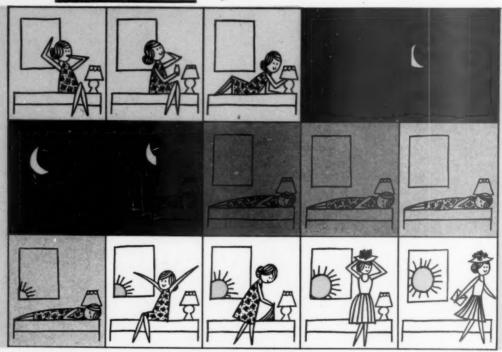
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BENDECTIN

at bedtime ?



prevents
morning sickness
here!

"... I have gained the best results with [Bendectin]... Because these tablets have a protective coating... the dose taken at night becomes effective in the morning."

NEW DOUBLE-BLIND STUDY SHOWS BENDECTIN EFFECTIVE IN 94% OF PATIENTS²

Medication	Number of patients	Complete relief	Partial relief	Failure
Bendectin	52	23 (44%)	26 (50%)	3 (6%)
		TOTA		
Placebo	57	13 (23%)	24 (42%)	20 (35%)
With the state	100 mg - 100	TOTAL 65%		124.7

"Bendectin was administered in a preliminary study to 146 patients and later, in a controlled, double-blind study to 52 patients, or to a total of 198 patients suffering from nausea and vomiting of pregnancy. A very gratifying therapeutic response was obtained in 178 or 90 per cent. In a double-blind portion of this study, the response of 52 patients treated with Bendectin was compared with that of 57 other patients treated with a placebo. In this group of 109 patients, there was a favorable response to Bendectin in 94 per cent and to the placebo in only 65 per cent."²

Measure Bendectin against your present Rx:

- Q. Has your present Rx been shown to relieve morning sickness before it starts in more than 9 out of 10 patients?²⁻⁵
- Q. Is your present Rx free of phenothiazine-like side effects and habituating properties?
- Q. Is it economical? Does it cost less per day, for example, than a quart of milk?

With Bendectin, the answer to all three is YES.

FORMULA:

DOSAGE: Two tablets at bedtime.

SUPPLY: Bottles of 100 and 500.

1. Middleton, T. F.: Postgrad. Med. \$4:699, 1958.

2. Geiger, C. J., et al.: Obst. & Gynec. 5:688, 1959.

3. Nulsen, R. O.: Ohio State M. J. 58:665, 1957.

4. Personal communications, 1956-57.

5. Towne, J. E.: Internat. Rec. Med. 171:583, 1958.

TRADEMARKS: BENDECTING, BENTYLG, DECAPRYNG



The Wm. S. Merrell Company Cincinnati, Ohio • St. Thomas, Ontario

for the silent syndrome*...

*the unmentioned edema, mood changes, GI distress, preceding menstruation

a comprehensive therapy

YCIFUNDENT STATE OF THE SYMPTOMS

for EDEMA...
CYCLEX provides the prompt diuresis of HYDRODIURIL for rapid reduction of weight gain, breast fullness, abdominal congestion

for MOOD-CHANGES...
CYCLEX supplies the effective relief of meprobamate for nervousness, irritability, tension, nausea, malaise, insomnia

for GI DISTRESS...
CYCLEX affords quick-acting relief of nausea and bloating associated with premenstrual tension.

INDICATION: CYCLEX is indicated for the relief of premenstrual tension with edema.

USUAL DOSAGE:

One CYCLEX Tablet 1 or 2 times daily, beginning when symptoms appear and continuing until the onset of menses.

of premenstrual tension

SUPPLIED: CYCLEX Tablets are supplied in bottles of 100. Each tablet contains 25 mg. of hydrochlorothiazide and 200 mg. of meprobamate.

Additional information on CYCLEX is available to physicians on request.

CYCLEX and HYDRODIURIL are trademarks of Merck & Co., INC.



MERCK SHARP & DOHME Division of Merck & Co., Inc. West Point, Pa.

In over five years



... for the tense and nervous patient

Despite the introduction in recent years of "new and different" tranquilizers, Miltown continues, quietly and steadfastly, to gain in acceptance. Meprobamate (Miltown) is prescribed by the medical profession more than any other tranquilizer in the world.

The reasons are not hard to find. Miltown is a known drug. Its few side effects have been fully reported. There are no surprises in store for either the patient or the physician.

s of clinical use...

Proven

in more than 750 published clinical studies

Effective

for relief of anxiety and tension

Outstandingly Safe

- 1 simple dosage schedule produces rapid, reliable tranquilization without unpredictable excitation
- 2 no cumulative effects, thus no need for difficult dosage readjustments
- 3 does not produce ataxia, change in appetite or libido
- does not produce depression, Parkinson-like symptoms, jaundice or agranulocytosis
- 5 does not impair mental efficiency or normal behavior

Miltown

Usual dosage: One or two 400 mg. tablets t.i.d.
Supplied: 400 mg. scored tablets, 200 mg. sugar-coated tablets; or as MEPROTABS*-400 mg. unmarked, coated tablets.

W WALLACE LABORATORIES / Cranbury, N. J.



WHEN EATING FOR TWO" BECOMES A WEIGHTY PROBLEM ...

You can often help expectant mothers cut down calories, yet boost milk nourishment, by suggesting PET *Instant* Nonfat Dry Milk.

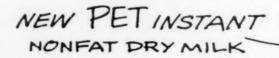
Liquid PET Instant has all the essential nourishment of whole milk except the fat. It's delicious as a beverage . . . takes the place of whole milk in cooking and baking without changing the flavor or texture of foods. And it has only half the calories of fresh milk.

Its generous amount of high-quality protein helps combat fatigue and excessive appetite, besides providing adequate calcium nutrition.

Your patients will like PET *Instant*. It tastes good, mixes instantly, and costs less than half as much as whole milk.



36.6% protein (in dry form). All the calcium and B vitamins of whole milk without the fat





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"PET"—Reg. U. S. Pat. Off. Copr., 1960, Pet Milk Co.

CONSISTENTLY GOOD CLINICAL RESULTS IN TRICHOMONAL AND MONILIAL VAGINITIS

TRICOFURON IMPROVED (Suppositories and Powder) cured 143 of 161 patients with vaginitis due to Trichomonas vaginalis, Candida (Monilia) albicans, or both. "Almost immediate symptomatic improvement was noted with the first insufflation."

Criteria for cure: freedom from infecting organisms as well as symptoms on repeated examinations during a three-month follow-up.

This cure rate of 88.8% is "surprisingly similar" to results reported by earlier investigators.

Coolidge, C. W.; Glisson, C. S., and Smith, A. S.: J.M.A. Georgia 48:167, 1959.

TRICOFURON

IMPROVED

2-step treatment brings swift relief, eradicates stubborn trichomonads, Candida (Monilia) albicans, Hemophilus vaginalis

1. Powder for weekly insuffiation in your office.

MICOFUR®, brand of nifuroxime, 0.5%

and FUROXONE®, brand of furazolidone, 0.1% in
an acidic water-dispersible base.

2. SUPPOSITORIES for continued home use

-1st week one suppository in the morning
and one on retiring. After 1st week, one
suppository at night may suffice.

Continue use of suppositories during menses.

Treatment should be continued throughout a complete menstrual cycle and for several days thereafter.

MICOFUR 0.375% and FUROXONE 0.25%

in a water-miscible base.

Rx new box of 24 suppositories with applicator for more practical and economical therapy.

Also available:

box of 12 suppositories with applicator.

NITROFURANS—a unique class of antimicrobials EATON LABORATORIES, NORWICH, NEW YORK



Each tablet contains:

DOSAGE: 1 tablet 1 or 2 times daily, 5-10 days before the period.

THE UPJOHN COMPANY / KALAMAZOO, MICHIGAN

CYTRAN GETS AT THE CAUSE

to restore hormonal balance...

corrective therapy Because Cytran contains the new progestin, Provera,† you can now reach the cause of premenstrual tension—hormonal imbalance. Estrogen-progesterone ratio is adjusted to more normal premenstrual balance. Thus even abdominal discomfort, shakiness, fatigue—symptoms incompletely controlled by mere symptomatic treatments—are effectively relieved.

to comfort the patient...

symptomatic therapy An effective diuretic (Cardrase†) and a mild tranquilizer (Levanil†) afford symptomatic relief while Provera works to effect a restoration of hormonal balance. They also supplement the activity of Provera in those rare cases where restoration of hormone balance does not completely eliminate edema and anxiety/tension.



Upjohn

OF PREMENSTRUAL TENSION



A"fitting" concern for the new mother ...time

A new baby in the family, whether the first or the fourth, makes it necessary for the whole family, particularly the mother, to adjust. For this, time is needed.

Your postpartum patient looks to you for advice on the best way to plan ahead.

Security-two ways

She experiences special physical comfort when you prescribe either the regular RAMSES® Diaphragm or the new RAMSES BENDEX,® an arc-ing type diaphragm.

The regular RAMSES Diaphragm, suitable for most women, is made of pure gum rubber, with a dome that is unusually light and velvet smooth. The rim, encased in soft abber, is flexible in all planes permitting complete freedom of motion.

For those women who prefer or require an arcing type diaphragm, the new RAMSES BENDEX embodies all of the superior features of the conventional RAMSES Diaphragm, together with the very best hinge mechanism contained in any arcing diaphragm. It thus affords lateral flexibility to supply the proper degree of spring tension without discomfort.

For added protection— RAMSES "10-Hour" Vaginal Jelly*

To give your patient the full protection of the diaphragm and jelly method—at least 98 per cent effective¹—RAMSES Jelly is uniquely suited for use with either type of RAMSES Diaphragm. It is not static, but flows freely over the diaphragm rim to add lubrication and form a spermtight seal maintained for ten full hours. It is nonirritating and nontoxic.

You can now prescribe a complete unit with either type of diaphragm. RAMSES "TUK-A-WAY" Kit #701 contains the regular RAMSES Diaphragm with Introducer and a 3-ounce tube of RAMSES Jelly; the #703 Kit contains the RAMSES BENDEX Diaphragm and Jelly. Each in attractive zippered case. At all prescription pharmacies.

Reference: 1. Tietze, C.: Proceedings, Third International Conference Planned Parenthood, 1953.

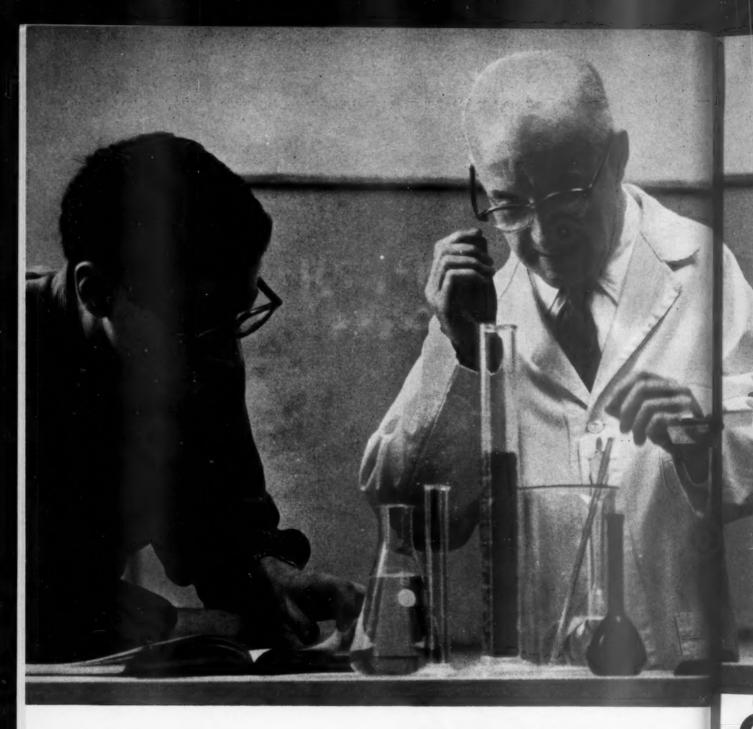
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*Active agent, dodecaethyleneglycol monolaurate 5%, in a base of long-lasting barrier effectiveness.

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greater loss of sodium lesser loss of potassium A new antihypertensive-saluretic, Hygroton, now enables still more effective longest in action... smoothest in effect control of hypertension and edema. more evenly sustained therapeutic response Because it is more prolonged in action than any other diuretic, Hygroton affords a smoother, more evenly sustained in hypertension and edema more nearly pure natriuretic effect Hygroton produces only minimal potassium loss . . . affords a better sodiumpotassium ratio than other saluretics.3 more liberal diet for the patient As a rule, with Hygroton, restriction of dietary salt is unnecessary. more convenience and economy For maintenance therapy three doses per week suffice to manage the vast majority of cases.2 in arterial hypertension Sustained control without side reactions. in edematous states Copious diuresis without electrolyte imbalance. Hygroton®, brand of chlorthalidone: White, single-scored tablets of 100 mg. in bottles of 100. (1) Stenger, E. G., et al.: Schweiz. med. Wchnschr. 89:1126, 1959. (2) Fuchs, M., Res: et al.: Current Therap. Research 2:11, January, 1960. (3) Ford, R. V.: Manuscript submitted for publication. Geigy, Ardsley, New York



just one prescription for keeps your hypertensives wide awake & working



ORETICYL®

(Oretic® with Harmonyl®)

gives them the benefits of: two effective ingredients

Oretic. Potent oral diuretic/antihypertensive producing maximum elimination of water, sodium, with minimum potassium loss.

Harmonyl. Fully as potent as reserpine in lowering blood pressure, Harmonyl has a lower incidence of such side effects as daytime lethargy, drowsiness, nasal stuffiness.

three precision dose forms

Oreticyl Forte. Oretic 25 mg., Harmonyl 0.25 mg. Recommended ''starter'' therapy

Recommended "starter" therapy in most cases of established hypertension. Usual dose: one t.i.d.

Oreticyl 25. Oretic 25 mg., Harmonyl 0.125 mg.

Oreticyl 50. Oretic 50 mg., Harmonyl 0.125 mg.

Either 25 or 50 strength recommended for adjustment of dose once response is seen. Dosage must be determined by patient's needs.

All 3 strengths, bottles of 100 and 1000.

ORETICYL—ORETIC WITH HARMONYL, ABBOTH
HARMONYL—DESERPIDINE, ABBOTH
ORETIC—HYDROCHLOROTHIAZIDE, ABBOTT
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STERILE Rib-Back BLADES. the surgeon's assurance of maximum cutting efficiency in every sterile blade package because... individual, puncture-resistant, reinforced foil packages further protect these traditionally sharper B-P Sterile RIB-BACK carbon steel blades. individual package design facilitates ease in opening -minimizing possibility of blade recontamination. individual unopened packages are ready for autoclaving-if desired. B-P RIB-BACK Blades are also available: RACK-PACK packages or 6 Blades of a size in BARD-PARKER COMPANY, INC. rust-resistant wrappers. DIVISION OF BECTON, DICKINSON AND COMPANY

PRINCE CONTROL VILLAGE CONTROL

"Thiosulfil" Forte

See over for therapy in difficult patients ▶

HOW TO IMPROVE THE PROGNOSIS IN THE DIFFICULT PATIENT WITH URINARY TRACT INFECTION: Proof of effectiveness and record of safety in long term therapy are two important factors in the selection of a sulfa, particularly when the infection is stubborn and recurrent; occurs during pregnancy; in prostatitis; in patients with indwelling catheters; when stasis is a potential cause of ascending infection. "Thiosulfil" Forte is specially valuable in the treatment of problem patients with urinary tract infection as demonstrated by years of clinical experience.

PROOF OF EFFECTIVENESS

In acutely infected patients: Results of seven years' clinical experience: Bourque's report covers 3,057 patients treated with "Thiosulfil" for upper and lower urinary tract infections. The causative organisms were E. Coli, Pseudomonas, Klebsiella, Enterococcus, Staphylococcus, Alcaligenes fecalis, and Proteus.

The results obtained were 76 per cent excellent; 11 per cent fair. In cystitis of short duration and without urinary obstruction 100 per cent good results were reported. average dosage: 3 Gm./day for 2 weeks

in pathologic conditions that cannot be cured 38 cases of chronic urinary tract infection:² "The cause of the infection in 25 cases was residual urine due to lower urinary tract disease, which for some reason could not be eliminated, such as prostatic carcinoma or hypertrophy (16 cases), vesical diverticulum or hypotonia (6 cases). Chronic upper urinary tract infection was present in 22 cases, some of which were secondary to the lower tract obstructive lesions."

"The results of treatment were as follows: Good, 17 cases, urine became clear and symptoms subsided while under treatment; fair, 10 cases, infection reduced and symptoms became less or subsided; poor, 11 cases, no evident change in urine or symptoms." initial dosage: 2 Gm./day

52 paraplegics with g.u. infections:³ "Urinalysis reverted to normal in 53 per cent of the 'Thiosulfil' group . . ."

"'Thiosulfil" was ineffective in only 7 per cent . . . " dosage: 2 Gm./day

RECORD OF SAFETY

Only these few side effects have been reported with "Thiosulfil." Out of 52 paraplegic cases . . . only one instance of dermatitis. Out of 50 cases . . . mild reactions consisted of slight gastric distress (1); flatulence (3); rash (1); pruritus (1); transient crystalluria (2). Out of 38 cases of chronic infection . . . mild reactions of: stomach and eye discomforts (1); dizziness (1); slight diarrhea (1). Out of 100 cases . . . one reaction—nausea. Out of 3,057 cases . . . 47 patients (1.6%) showed g.i. disturbances and 33 patients (1.1%) allergic reactions. Out of 300 cases . . . one reaction (appetite loss and lassitude). NO REPORTS OF: hemorrhagic dyscrasias, hematuria, anuria, agranulocytosis.

The Sulfa Compound Used Successfully Without Interruption for: one month; ^{3,4} more than 6 weeks; ² 90 days; ⁵ 18 months; ³ 5 to 6 years. ⁷

DOSAGE (Urinary Tract Infections)

TIME PERIOD	DOSE
First two weeks	3 Gm./day ¹
2 weeks to 3 months	2 Gm./day ^{3,4}
3 months or longer	0.5 Gm./day ⁷

Suggested Range of Dosage: 1 or 2 tablets three or four times daily. Note: The usual precautions exercised with sulfonamides should be observed. Supplied: No. 786—Bottles of 100 and 1,000 scored tablets. Each tablet contains 0.5 Gm. sulfamethizole.

References—1. Bourque, J-P., and Gauthier, G-E.: Seven years' experience with sulfamethizole, to be published. 2. Barnes, R. W.: J. Urol. 71:655 (May) 1954. 3. Cottrell, T. L. C., Rolnick, D., and Lloyd, F. A.: Rocky Mountain M. J. 56:66 (Mar.) 1959. 4. Bourque, J-P., and Joyal, J.: Canad. M.A.J. 68:337 (Apr.) 1955. 5. Hughes, J., Coppridge, W. M., and Roberts, L. C.: South, M. J. 47:1082 (Nov.) 1954. 6. Goodhope, C. D.: J. Urol. 72:552 (Sept.) 1954. 7. Hughes, J., Coppridge, W. M., and Roberts, L. C.: North Carolina M. J. 17:320 (July) 1956.

THE SULFA COMPOUND THAT IS ESPECIALLY VAL-UABLE IN URINARY TRACT INFECTIONS BECAUSE IT CAN BE GIVEN SAFELY—WITHOUT INTERRUP-TION—FOR WEEKS, MONTHS...EVEN YEARS.

"Thiosulfil" Forte

AYERST LABORATORIES, NEW YORK 16, N.Y., MONTREAL, CANADA

"life saving" in many cases...

KANTE EN Kanamycin Sulfate Injection

...a highly potent, bactericidal antibiotic for combating staph and gram negative infections

"There appears to be no doubt that kanamycin has been lifesaving in those instances in which organismal resistance precludes the use of other antimicrobials."* Well tolerated when used on a properly individualized dosage schedule which does not induce excessive blood levels.

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*Council on Drugs, J.A.M.A. 172:699, 1960

Information on dosage, administration and precautions contained in official package circular, or available on request.

SUPPLY: KANTREX Injection, 0.5 Gm. kanamycin (as sulfate) in vial containing 2 ml. volume. KANTREX Injection, 1.0 Gm. kanamycin (as sulfate) in vial containing 3 ml. volume.

BRISTOL LABORATORIES SYRACUSE NEW YORK

Safe and Sand Sound in any pregnancy

to prevent morning sickness

With new Tigan 250 mg capsules you can now provide protection against morning sickness with only two capsules daily—one at bedtime and one in the morning. Tigan is so safe that it may be used with confidence as a routine prescription in any pregnancy. Avoiding the risks of phenothiazine derivatives and the limitations of the antihistamines, Tigan acts both therapeutically and prophylactically to stop active vomiting or to prevent nausea and vomiting.

Consult literature and dosage information, available on request, before prescribing.

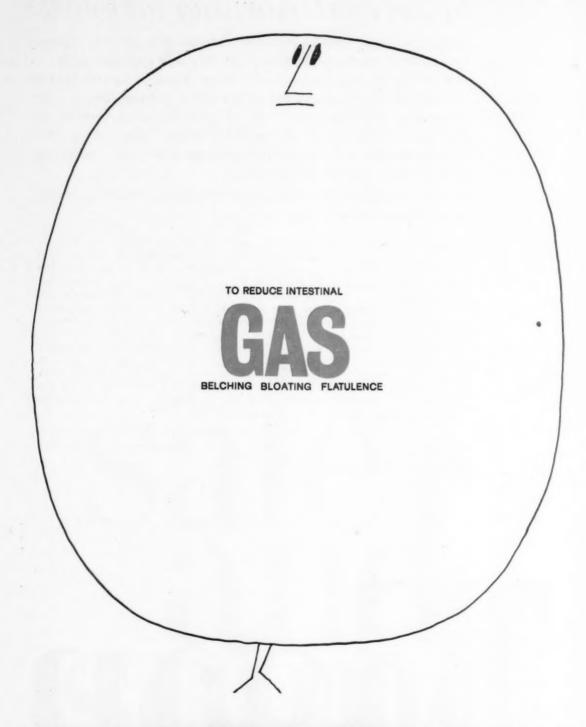
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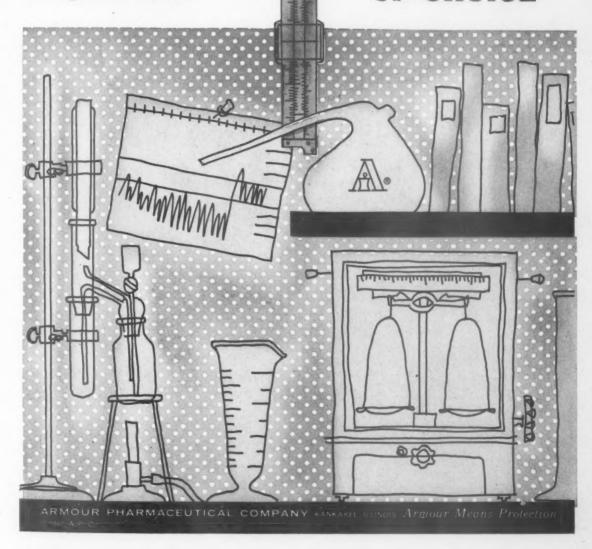
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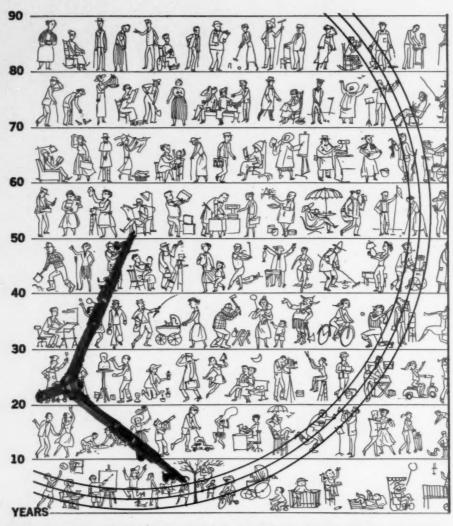
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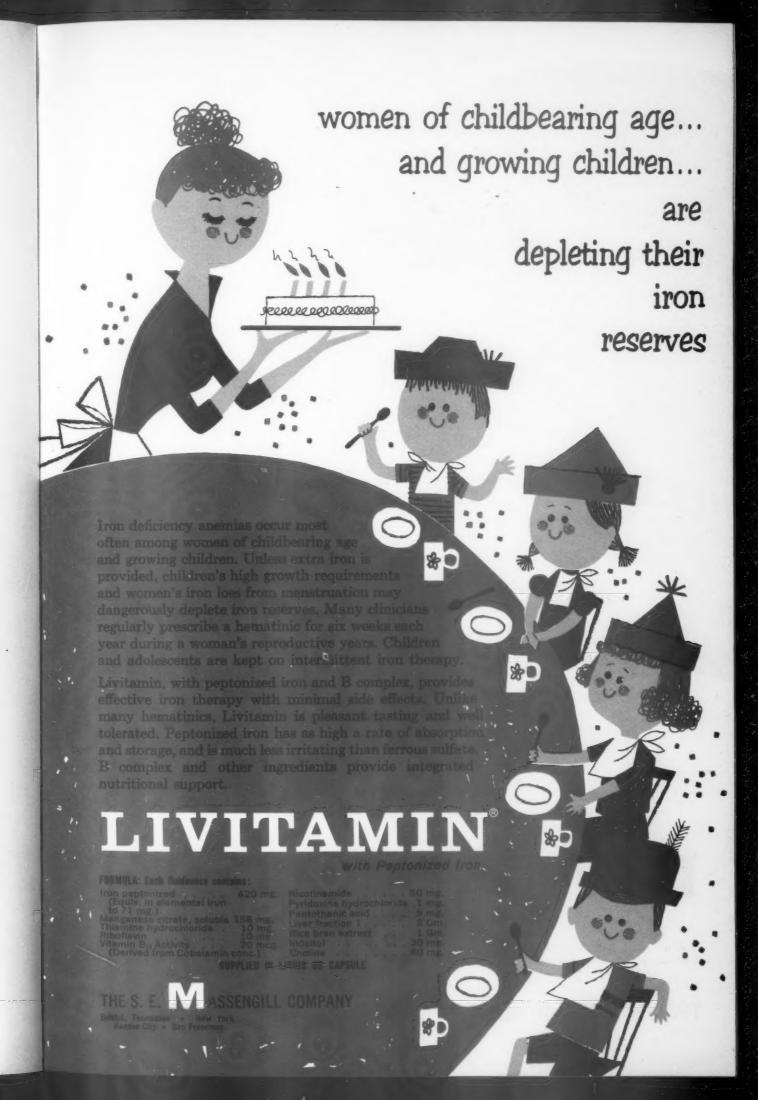


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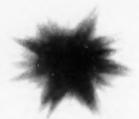
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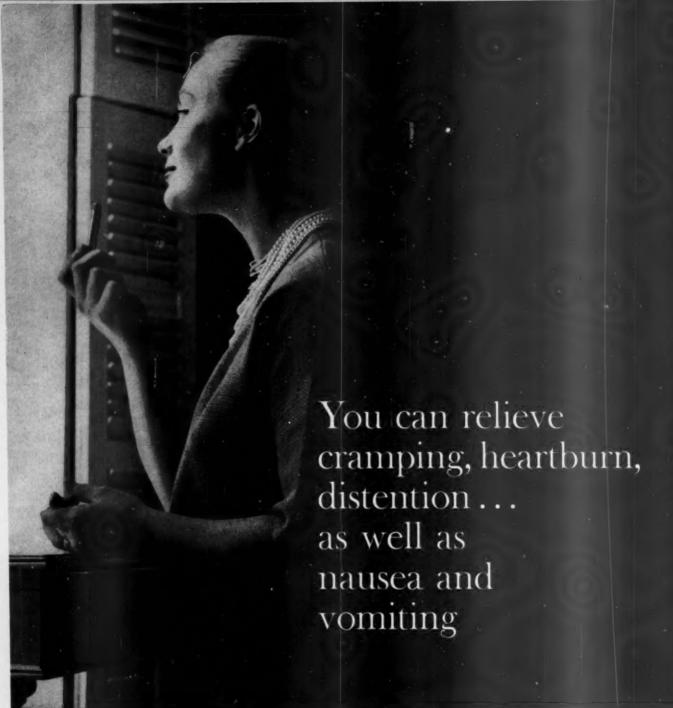
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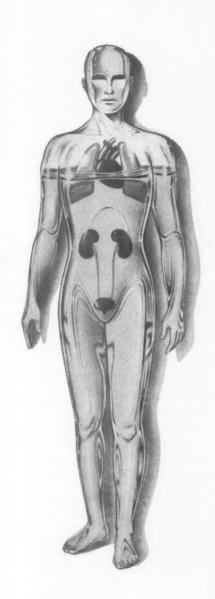
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American Journal of Obstetrics and Gynecology

GYNECOLOGY

Mesonephric clear cell carcinoma of the ovary: a clinical and pathologic study

THOMAS M. PARKER, M.D.

MALCOLM B. DOCKERTY, M.D.

LAWRENCE M. RANDALL, M.D.

Rochester, Minnesota

A M O N G the many and varied histopathologic patterns observed in primary carcinoma of the ovary is one featuring a preponderance of columnar cells with water-clear cytoplasm arranged in a pattern strikingly similar to that in the classic renal hypernephroma. First described by Peham³ in 1899, this clear cell carcinoma continues

to resist attempts to define its histogenesis adequately. Originally interpreted in the light of the Grawitz hypothesis, it soon became confused with other "clear cell" lesions of the ovary, particularly the masculinizing tumors of "true" adrenal rest origin and some of the luteinized tumors. By the time separation from these entities had been achieved, the Grawitz hypothesis had been rejected and it became necessary to search for a more adequate foundation on which to base a histogenetic concept.

Such a modernized concept of histogenesis was introduced by Saphir and Lackner,4 in 1944, who proposed an origin in misplaced mesonephric tubules present in the ovary as a result of the juxtaposition of gonad and mesonephros at the 7 mm. stage of embryogenesis. The ovarian tumor then

Abridgment of thesis submitted by Dr. Parker to the Faculty of the Graduate School of the University of Minnesota in partial fulfillment of the requirements for the degree of Master of Science in Pathology.

From the Departments of Pathology, Surgical Pathology, and Obstetrics and Gynecology, Mayo Clinic and Mayo Foundation.

The Mayo Foundation is a part of the Graduate School of the University of Minnesota.

became a "kidney cell" cancer and should be properly identified as "hypernephroid" in line with the modern principles of the origin of renal carcinoma. Essentially, Saphir and Lackner employed a principle of neoplasia in ovarian mesonephric rests in the same way that Schiller,⁵ 5 years before, had defined the tumor that he called "mesonephroma ovarii."

More recently, however, it has been suggested that the ovarian clear cell tumors originate in a tissue more primitive than mesonephros. This viewpoint has been designed to overcome the fact that it is the metanephros (not the mesonephros) which eventually gives rise to the definitive kidney. Some general agreement has been reached that the hypernephroid carcinoma arises in premesonephric mesodermal tissue. What has not been agreed on, however, is the relationship between this lesion and the socalled mesonephroma of Schiller. Two schools of thought have arisen with respect to this problem. The one, championed by Novak and associates,2 and later by Stowe,8 affiliates the clear cell carcinoma with Schiller's mesonephroma and suggests a common histogenesis and pathogenesis for both. The other supports Teilum's10 claims that the clear cell tumors (along with certain related variants) are the only tumors of mesonephric mesodermal origin. Schiller's mesonephroma, losing its mesonephromatous membership, now becomes a germ cell tumor that Teilum¹⁰ termed an "extraembryonic mesoblastoma of germ cell origin."

To date, approximately 35 primary nonsecretory clear cell ovarian carcinomas have been reported from available sources. Aside from the striking hypernephroid histologic appearance of these tumors, there has been nothing that would tend to separate them either clinically or pathologically from the more common primary ovarian carcinomas of other types. Thus, the literature has shown that hypernephroid ovarian tumors usually occur around the end of the fifth decade of life and that they are associated with a grave (although by no means hopeless) prognosis entirely comparable to that to be expected of "ordinary" ovarian carcinoma showing similar degrees of dedifferentiation. The 35 tumors have been divided approximately evenly between right and left ovaries, and they have appeared as bilateral lesions in a few cases. Cystic and solid lesions have been reported with approximately equal frequency. Attempts to define the nature of the clear cytoplasm with special staining techniques have resulted in inconstant and variable findings.

We wish to report our experience with tumors of this type observed at the Mayo Clinic from 1925 through 1954.

Materials and methods

Since microscopic sections of these tumors had been filed at the clinic under the general designation of "ovarian carcinoma" without a qualifying phrase, it was necessary to search through the entire group of ovarian carcinomas in order to select those in which clear cells composed the major histologic feature. By holding to this criterion, it was possible to discover 26 such tumors out of 1,192 primary ovarian carcinomas. The incidence of primary clear cell ovarian carcinoma in this study was, therefore, a little more than 2 per cent of all ovarian carcinomas. A total of 24 patients were involved, since the lesions were bilateral in two instances.

Of these 24 patients, 17 had undergone removal of the primary lesion at the clinic; consequently, slides and also the original tissues were available for study in these cases. The remaining 7 patients had undergone resection of the primary tumor elsewhere, but a sufficient number of representative sections were available to qualify the lesions for acceptance in the study. Detailed clinical records were available in all 24 cases.

The clinical records were reviewed and a follow-up program was initiated. The gross specimens, which had been preserved in a 10 per cent solution of formalin, were obtained and examined. Multiple blocks were cut from each tumor, and the ancillary pathologic changes were sampled when indicated. Blocks embedded in paraffin were sectioned



Fig. 1. Solid right ovarian carcinoma in coronal section. The polypoid superior portion is a solid clear cell carcinoma that connects with the inferior larger parvilocular portion at a plane deeper than that of this picture.

and stained with hematoxylin and eosin as well as with Mayer's mucicarmine. Additional blocks of tissue were cut for frozen section, and these were subsequently cut and stained for neutral fats with Sudan IV. No attempt was made to demonstrate the presence of glycogen in view of the fact that the tissues had been preserved for a considerable time in formalin.

Necropsy had been performed in 3 cases in the series after operation. The protocols as well as the histologic material from these examinations were reviewed in a similar fashion.

Clinical features

The ages of the patients when the tumors were discovered ranged from 37 to 68 years; the average for the group was 53 years, and a surprisingly close grouping around this mean value was evident. When the criterion of multiple familial carcinoma was defined as the occurrence of three or more malignant tumors in the immediate family (grandparents, parents, siblings, or children), it was found that 5 patients in this series had such pedigrees. Of the 24 patients, 14 were nulliparous.

Positive physical findings were confined

in most cases to a palpable pelvic mass, although one patient had a synchronous squamous cell carcinoma of the anal skin. Other physical findings appeared unrelated. Routine studies on blood and urine were unremarkable with the exception of a uniformly increased erythrocytic sedimentation rate in those patients who came to the clinic without having undergone any previous surgical attack on the primary lesion.

Treatment in most instances consisted of total abdominal hysterectomy with bilateral salpingo-oophorectomy and a postoperative course of roentgen therapy. Two of the more recently treated patients received intraperitoneal treatment with radioactive gold after operation.

Follow-up studies were obtained on 21 of the 24 patients: 14 were dead, 2 were living with recurrences, and 5 were alive and well, all 5 having survived for 5 or more years after resection of the primary tumors. Thus, 24 per cent of the group have enjoyed 5 year cures. As might be expected, the finding of either neoplastic extension within the pelvis or distant implantation betokened a rapid death. Implantation was found in both patients who had bilateral tumors, and a total of 7 patients presented evidence of advanced disease. Six of these died early, usually within a year from the date of operation. Follow-up was unsuccessful on the seventh patient.

Gross pathologic features

From the records, it was possible to ascertain the location of 25 of the 26 tumors. The seat of the lesion was the right ovary in 9 cases and the left ovary in 12. As already noted, 2 patients had bilateral tumors. Normal ovarian tissue could not be identified grossly in any instance because all of the lesions had attained such a size as to destroy the evidence of their origin. Thus, the exact anatomic site in terms of ovarian anatomy could not be determined.

An original gross surgical description of the primary lesion was obtainable in 23 instances; 14 lesions were essentially cystic



Fig. 2. Histologic patterns in mesonephric clear cell ovarian carcinoma. a, Sheets of clear cells supported on a delicate connective tissue stroma. Such a zone represents the alveolar pattern. b, The finding of cellular pleomorphism, as in this section, is unusual. Note the focus of cells with granular cytoplasm at the right. c, Note the "peg cells" lining connective tissue septa at the lower left. Papillary stalks of clear cells are seen at the right. d, Delicate papillary fronds with fine connective tissue cores. (Hematoxylin and eosin. ×90.)

tumors, while the remaining 9 were solid. The tumors were of the solid type in the 2 patients who had bilateral involvement. Grossly, the preserved cystic tumors could not be distinguished from cystadenocarcinomas of the more common types. Intracystic growth, intramural growth, and sometimes extramural papillary and solid growth were features of these clear cell carcinomas, just as they are in ordinary ovarian carcinoma. It was impossible to determine color in these specimens in view of the deterioration of this quality with preservation in formalin. It was thus impossible to verify the commonly described vellow color of the fresh solid portions. Necrosis was an especially frequent gross finding, particularly in the solid tumors. Secondary cystic degeneration and calcification were each found once among the solid tumors.

Of great interest was the gross finding, in 3 solid tumors only, of minute cysts visible on extremely close inspection of the cut surface. These tiny cysts appeared to be embedded in a dense stroma of fibrous consistency when viewed with a hand lens. In two instances, this finding was restricted to certain portions of the tumor, the remaining tissue being softer and more homogeneous; in the third case, this microcystic alteration was present in only one of the tumors of a bilateral pair, the contralateral lesion being homogeneous. Microscopic examination bore out the suspicion that these "spongy" zones were compatible with what Schiller6 described in 1943 as parvilocular tumors of the ovary. Particularly impressive was the tumor illustrated in Fig. 1, in which the hard inferior portion of the growth was parvilocular, while the soft superior extension was a solid epithelial clear cell neoplasm.

Study of the uterus, tubes, and contralateral ovary in available specimens revealed only the usual pathologic entities commonly noted in women of this age group. Thus, multiple fibromyomas, endometrial and cervical polyps, and various types of benign cysts of the contralateral ovary were encountered. In two cases, implants of tumor were found on the posterior uterine wall.

Microscopic features

Whatever portion of the tumor was sampled, the sections stained with hematoxylin and eosin strikingly revealed the clear cell composition (Fig. 2, a). For the most part, cells and nuclei were uniform in size and shape, although a rare lesion showed cellular pleomorphism (Fig. 2, b). Careful search sometimes revealed small clumps of cell with acidophilic cytoplasm; seldom numbering more than 10 or 20 cells, these clumps usually merged into other clusters of cells more typically vacuolated (Fig. 2, b). Clear cells, particularly those lining a tubular or cystic space, sometimes became partially separated one from the other, taking on the appearance of the "peg" cells described originally in association with Schiller's mesonephroma ovarii (Fig. 2, c). Such cells could be identified in 5 lesions, and their transition into typical clear cells always was noted. With the exception of the parvilocular zones, the stroma usually was extremely delicate and highly vascular, particularly where an alveolar or a papillary pattern was present (Fig. 2, d). However, 2 tumors in the series had a stroma composed of primitive-appearing mesenchymal tissue, from which it was apparently possible to observe the genesis of clear cells (Fig. 3).

The manner in which the individual cells combined to form the architectural pattern

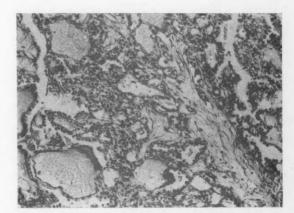


Fig. 3. From the primitive mesenchymal stroma seen at the right appear to arise clear cells that are being grouped in tubular fashion at the left. (Hematoxylin and eosin. ×90; reduced approximately 1/4.)

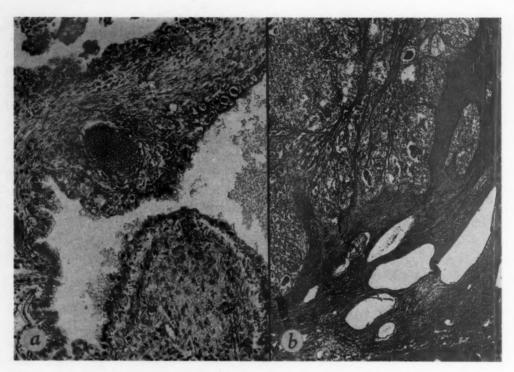


Fig. 4. a, Ovarian hypernephroid tumor. Note the "dichotomous" tubular branching at the lower left. (Hematoxylin and eosin. ×95.) b, This section was taken from the line of junction between the inferior and superior portions of the tumor illustrated in Fig. 1. Note the dense masses of clear cells at the upper left and the parvilocular pattern at the lower right. (Hematoxylin and eosin. ×27.)

was quite varied. In general, it was possible to recognize tubular, parvilocular, papillary, and alveolar designs. It was hypothesized that the basic potential of the clear cell was to line tubular and cystic spaces. With increased aggressiveness, the clear cell lining of these spaces proliferated in a papillary fashion so as to fill the lumen entirely and thus produce a nest or sheet of clear cells characteristic of the alveolar pattern. It was in association with this latter pattern that necrosis was observed most commonly. Although it is relatively easy to dissect out all of these patterns for descriptive purposes, it must be emphasized that seldom did a tumor display a pure example of any one specific design. In practically every instance, if a sufficient number of blocks were taken, it was possible to discover an intermingling of 2 or more of these patterns. Thus, the alveolar and the papillary pictures were identified 19 and 20 times, respectively, and tubular structures formed part of the histologic appearance in 24 lesions. Although the parvilocular pattern was pronounced in the 3 specific instances in which its presence was suspected grossly, it could be identified at the microscopic level in 7 more instances. In only one case could the peculiar bifid tubular branching, described as "dichotomous" by Teilum, be identified (Fig. 4, a). On the basis of Broders' classification, the malignancy of all lesions was considered to be Grade III or IV.

Special attention was paid to the parvilocular tumors. Microscopically, such zones were composed of rather widely separated, large, tubular, and cystic spaces surrounded by dense connective tissue. In some areas, the spaces were lined by a low, almost flattened, epithelium; in others, the epithelium was more cuboidal. At times, such epithelium had the distinct appearance of "peg" cells although the cytoplasm was usually more abundant than it is in the prototype of this architecture in mesonephroma ovarii.

That these lining cells were essentially the same as clear cells became obvious when the parvilocular zones merged into areas of typical homogeneous clear cell neoplasm as a result of hyperplasia of the epithelial component at the expense of the stroma (Fig. 4, b). From these observations, it appeared that the clear cell and parvilocular neoplasms were, if not identical, at least closely related lesions.

Careful review of the sections from the standpoint of classification failed to disclose a tumor that presented zones which could be justifiably designated as the mesonephroma of Schiller. Although the tubular pattern, often in association with "peg" cell epithelium, was encountered commonly, other stigmas of the so-called mesonephroma ovarii were consistently absent. Thus, the glomeruloid structure with a central and single capillary loop, and the loose embryonal network of endothelium-like cells (the two essential features of Schiller's tumor) were not seen. However, the selection of our cases was such as to exclude, or tend to exclude, growths of other than a clear cell composition.

The results of special staining techniques were disappointing. With neither Sudan IV nor the mucicarmine stain could a consistent trend be demonstrated in the 19 tumors so treated. For example, although frozen sections stained with Sudan IV showed the presence of fat in all of these cases, in only 2 lesions could neutral fat conceivably have been the cause of the cytoplasmic clarity of the clear cell, for in only those 2 cases was a significant amount of cytoplasmic fat demonstrated. In all others, the fat lay in obvious relationship to zones of necrosis, with only minimal amounts, if any, seen in viable tumor cells. In further support for a necrotic cellular origin of most of the fat was the common finding of sudanophilic material within macrophages in the connective tissue stroma adjacent to necrotic zones.

As far as indicating the nature of the intracytoplasmic substance, stains for mucin were likewise inconclusive. In some lesions, a faintly positive reaction was elicited in the cytoplasm of the clear cells; most of the tumors, however, reacted negatively. The one exception to this general observation was in the parvilocular zones, in which carminophilic substances were prominent. The reaction for mucin was pronounced within the lumina of the cysts and also in their lining epithelium. However, this reaction disappeared where the parvilocular architecture merged into solid clear cell carcinoma.

A review of the necropsy reports and the histologic material obtained at necropsy in the 3 patients who died after operation failed to reveal any evidence of renal disease. Two of these patients died of peritonitis, and the third died of abdominal carcinomatosis.

Comment

The general clinical and prognostic observations drawn from this study agree with the over-all picture presented in the literature since Peham's original report. Primary ovarian clear cell carcinoma is a rare lesion, accounting for only 2 per cent of all primary ovarian carcinomas. It tends to occur in women in the fifth and sixth decades of life. The right and left ovaries are involved with equal frequency. Cystic and solid tumors are represented, and some lesions are bilateral. The prognosis should be guarded, and it is about the same as that of carcinoma of the ovary in general for comparable grades of malignancy. Of interest was the finding of an apparently increased incidence of a family history of malignant tumors, as well as of a high level of infertility, in the group. Such phenomena have been noted before in comparable series. In general, whatever peculiarities these tumors may possess apparently are not manifested in terms of the clinical and prognostic picture.

Since 1946, Teilum has concerned himself with the taxonomic problems posed by Schiller's mesonephroma and clear cell carcinoma of the ovary. He has remarked on the extremely specific histologic criteria set up by Schiller for the diagnosis of mesonephroma ovarii. He also has noticed the fact that many of these tumors have occurred in

younger women, five of the 10 patients in Schiller's original group being less than 30 years of age. In addition, the "Schiller tumor" has been found occasionally to contain both dysgerminomatous and trophoblastic elements. Furthermore, Teilum has described histologically identical lesions arising in the male gonad. Therefore, Teilum contended that the mesonephroma of Schiller is not of mesonephric origin but rather is a germ cell tumor intermediate between dysgerminoma and chorionepithelioma, the entire group being called the "gonocytoma" series. To add further support to his beliefs, Teilum cited the confusion that existed between Schiller's mesonephroma and similar but unrelated lesions. This confusion caused Schiller6 to publish his paper on parvilocular tumors of the ovary, in which he clearly separated the mesonephroma ovarii from the parvilocular lesions; as recently as 1957, Schiller and associates have re-emphasized this distinction.

In 1946, Teilum9 described a "true" mesonephric ovarian carcinoma occurring in a 45-year-old woman who died of metastatic involvement one year after resection of the tumor. Histologically, it revealed a primitive mesenchyme that appeared to generate clear cells, the latter being associated with a branching tubular pattern. At one end, the tubules enlarged into flask-shaped dilatations; at the other end, they branched in a bifid manner that he described as "dichotomous." In later articles, 10, 11 Teilum related this tumor to the parvilocular growths and, through the latter, eventually to clear cell carcinomas. Thus, in 1954, he11 grouped parvilocular tumors, clear cell carcinomas, and the specific embryonal tumors described above under the common classification of mesonephric carcinoma. Clear cell carcinoma of the ovary, then, may be considered a prominent member of the mesonephric carcinomas.

The other viewpoint adopted recently with regard to this problem is the one enunciated by Novak and associates² in 1954. These authors contended that the Schiller tumor should be amalgamated with the clear

cell and parvilocular tumors and that the entire group should be considered mesonephric in origin. They thought that too much stress had been placed on Schiller's "glomeruloid" structures, and that all these tumors are basically similar histologically. The transition of clear cells to "peg" cells and vice versa was cited by Stowe⁸ as further evidence of the common identity of these tumors. Novak's group, as well as Stowe, have accepted a matrix less differentiated than the mesonephros as the tissue of origin for tumors of this group and have accepted the mesonephroma and the clear cell carcinoma as related lesions.

Since this study has concerned itself with only the clear cell variant of Teilum's group of mesonephric carcinomas, the conclusions drawn obviously pertain only to this specific lesion. This possibly represents an advantage in that it avoids the problem of adulteration of the series with questionable lesions. Certainly, these clear cell carcinomas are a homogeneous group from both histologic and clinical viewpoints. There are no clinical findings to separate patients who have such tumors from patients with the commoner histologic types of carcinoma. On the other hand, this group does not appear to be compatible with the group of patients who have Schiller's mesonephroma, which (as Schiller's original article pointed out) afflicts children and young adults in half the cases.

The inability to discover in any of our clear cell carcinomas microscopic zones diagnostic of the Schiller tumor is in support of Teilum's beliefs. Also, the lack of teratomatous or embryomatous areas in any of our clear cell tumors appeared out of line with findings in the Schiller tumor, for the lesions in Schiller's Cases 9 and 10 were found in association with a dermoid and a dysgerminoma, respectively. The affiliation of clear cell carcinoma with parvilocular carcinomas, suggested by Teilum, is substantiated in our series.

Mesenchymal stroma giving rise to clear cells was seen in 2 tumors only, and dichoromous branching was indentified in one of these. These are characteristics of mesonephric carcinoma according to Teilum, but their essential significance remains to be established more fully. The inconsistent reactivity of Sudan IV and mucicarmine stains in our series indicates that elucidation of the basic nature of the cytoplasmic clarity of these neoplastic clear cells must await further study on a more sophisticated histochemical scale.

Clear cell carcinoma of the kidney may involve the ovary secondarily. That such an occurrence is rare is attested to by the fact that Lucké and Schlumberger1 stated that such metastatic tumors accounted for only 0.3 per cent of all metastatic lesions arising from renal carcinoma. There are 3 reported cases in which such secondary tumors presented as primary ovarian lesions. All these ovarian metastatic tumors occurred after prior nephrectomy for hypernephroma, the time interval varying from 19 months to 11 years. In 3 of our patients, absolute proof was available that the ovarian lesions were primary. In none of the other patients was there any evidence to suggest otherwise.

Summary and conclusions

A study was made of 26 malignant tumors of the ovary selected on the basis of their predominant clear cell morphology. These tumors were found in 24 women encountered during a 30 year period at the Mayo Clinic. Such lesions represent approximately 2 per cent of all ovarian carcinomas.

These patients could not be distinguished clinically from any other group of patients with solid and cystic ovarian carcinomas of the higher histologic grades of malignancy.

A 24 per cent 5 year cure rate was noted in this series, although extension, implantation, and bilaterality suggested a considerably worse prognosis.

Varied histologic patterns prevailed in these clear cell carcinomas, and intertransformations were common among them. The parvilocular carcinoma of the ovary is a member of this clear cell group.

A connection between clear cell ovarian carcinoma and the mesonephroma of Schiller could not be established.

A premesonephric mesodermal tissue origin for these tumors appears reasonable.

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Hypernephroid carcinoma of the ovary

Case report

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HYPERNEPHROID carcinoma or clear cell adenocarcinoma of the ovary is a rare disease entity. Just how rare it is is difficult to determine from the literature but only two small series, 1, 2 in addition to a few isolated case reports, have come to our attention. This is the only case recorded in the files of the Hertzler Clinic in the last 20 years, during which time approximately 8,000 pelvic laparotomies have been performed, nearly 500 of them for ovarian pathology.

The hypernephroid carcinoma of the ovary is a bright yellow, nonmasculinizing, malignant tumor which differs histologically and symptomatically from either the luteoma or the hypernephroma of the ovary. According to Saphir and Lackner1 the tumor is believed to take origin from persistent tubular structures of intraovarian mesonephric origin and is in most respects similar to the hypernephroid carcinoma of the kidney. The latter neoplasm, endocrinologically inert, is also a yellowish malignant tumor but arises within the kidney and is believed to originate from kidney tubules and not from suprarenal structures. Since the histologic architecture of the clear cell adenocarcinoma of the ovary resembles suprarenal tissue but the cells do not arise from suprarenal cells, it is called hypernephroid (resembling suprarenal cortical structures) carcinoma rather than hypernephroma.

From the Hertzler Research Foundation and the Hertzler Clinic.

A detailed case report of one such neoplasm follows:

Mrs. E. D., a 65-year-old white woman, complained of painless swelling of the abdomen for 6 weeks prior to admission to the Hertzler Clinic. She was referred by her local physician with the diagnosis of fibroid tumor of the uterus, with a recommendation for operation. Her previous medical history revealed a late marriage with no pregnancies, no previous operations, and only 2 medical illnesses requiring hospitalization. One of these admissions was concerned with asthma and bronchiectasis and the other with glaucoma and diverticulosis of the colon. The patient had had an uneventful menopause at 52 years of age and had experienced no vaginal bleeding or discharge since.

Physical examination revealed an alert white woman in apparently good health, with a normal pulse rate, respiration, and temperature; she had a mild degree of hypertension. The positive physical findings consisted of moist râles in the right lung base, hypertension, and a grapefruit-sized cystic but firm midline pelvic mass felt both abdominally and by bimanual examination. A provisional diagnosis of ovarian cyst, bronchiectasis, glaucoma, and benign hypertension was made. There was no evidence of virilism.

The following laboratory tests were within normal limits: complete blood count, urinalysis, serology, transaminase, blood urea nitrogen, fasting blood sugar, protein-bound iodine, gastric analysis, bleeding time, coagulation time, platelet count, total protein and albumin-globulin ratio, cholesterol, intravenous pyelogram, gall bladder visualization, barium meal, and electrocardiogram. The pyelogram, while normal, revealed a mass the size of a large grapefruit in the

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pelvis; x-ray examination of the chest showed a lobulated diaphragm; barium enema confirmed a previous diagnosis of multiple diverticula scattered throughout the sigmoid and descending colon. On cystoscopic examination a large extrinsic noninvasive mass was seen to be pressing in upon the bladder.

The diagnostic impression after completion of the examination remained benign hypertension, glaucoma, bronchiectasis, and a pelvic mass. Exploratory operation was advised and accepted. At operation a large 13.5 by 11 by 7 cm. bluish left ovarian cyst with attached tube was encountered and removed intact along with the uterus and the contralateral tube and ovary. Exploration of adjacent lymph nodes proved them benign. Exploration of the remainder of the abdomen revealed a walled-off perforated diverticulum. This was removed and the patient's abdomen was closed in a routine manner. She had an uneventful recovery and left the hospital in 10 days. She has been seen several times in the past year on routine postoperative follow-up visits and remains well.

Gross pathology. The ovarian tumor, measuring 13.5 by 11 by 7 cm. and weighing 360 grams, had a glistening bluish gray lobulated surface. An 11 cm. long tube was stretched out over the surface of the tumor. In one area yellow nodules protruded from the wall without perforating the capsule (Fig. 1, A). The cyst contained about 100 c.c. of clear, straw-colored fluid. On cross-section the wall of the cyst was thin, measuring between 1 mm. and 2 mm. with two large tumors firmly attached (Fig. 1, B). These two tumors filled out three fourths of the cavity of the cyst. One tumor measured 7 by 5 cm., had a deep yellow color, and was completely solid. There was no hemorrhage or necrosis visible. The other tumor, measuring 8.5 by 6 cm., consisted of many small cystic spaces filled with clear, straw-colored fluid. This second tumor appeared to be a separate tumor and touched the yellow tumor in only one area. On cut section the wall of the second cyst varied between 1 mm. and 1 cm. in thickness, and the tissue was grayish brown in color.

Microscopic pathology. Section of the thin cyst wall (Fig. 2) showed fibrous tissue which was quite cellular near the lumen. The epithelial lining was in a single layer and consisted of cuboid cells of varying sizes. The nuclei did not protrude over the surface of the cells, some of which had a clear cytoplasm. No cilia were

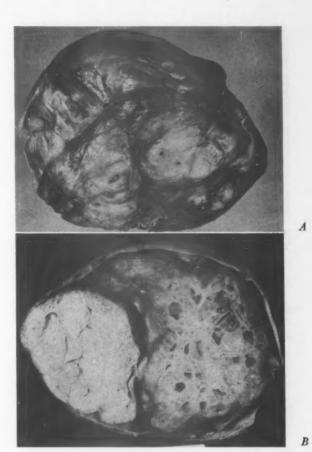


Fig. 1. Hypernephroid carcinoma of the ovary. A, Photograph of gross specimen. B, Cross-section of the tumor.

seen on the internal surface of the cells. Section of the yellowish tumor (Fig. 3) showed the typical structure of hypernephroma. The tumor cells were clear and had a very distinct cytoplasm. The nuclei, which were found in the center of the cells, were dark stained and varied markedly in size. Most of the cells were arranged in small glandular spaces while others formed papillae with a very thin fibrous stalk. The stroma was very scanty and consisted only of blood vessels with fibrous tissue. The other tumor (Fig. 4) consisted of a great many glandular spaces which varied in size and had the appearance of mesonephroma. The lining cells had protruding nuclei which varied in size. The cytoplasm was either light stained or granular. Occasional tufts which originated from the wall were seen protruding into the lumen. These tufts were covered with hobnail epithelium and contained few blood vessels. The tumor apparently invaded the stroma.



Fig. 2. Hypernephroid carcinoma of the ovary. Wall of large cyst; cuboid epithelium without cilia.

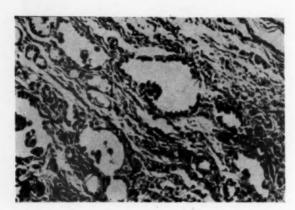


Fig. 3. Hypernephroid carcinoma of the ovary; clear cells with distinct cell border.

Diagnosis. Hypernephroid carcinoma and mesonephroma in an ovarian cyst.

Comment

It is highly important, of course, to determine whenever possible that such malignant growths as these are not really metastatic in nature. As far as can be determined, the case under discussion is that of a primary lesion. The opinion from our departments of urology and radiology, following complete examination preoperatively and postoperatively and including intravenous and retrograde pyelography, is that the kidneys are innocent. It is admitted that this is not proof positive but it is the best evidence obtainable under the circumstances.

There is another rare yellow malignant tumor which masculinizes and which is thought by some to arise from misplaced suprarenal cortical cells within the ovary, hence, hypernephroma. This tumor is also called a luteoma or lutein cell blastoma since others believe that the tumor arises from luteinized granulosa cells rather than from misplaced suprarenal cells. The tumor, regardless of origin, produces masculinizing characteristics such as amenorrhea, voice changes, hirsutism, and hypertrophy of the clitoris indistinguishable from similar disturbances in sex characteristics produced by the arrhenoblastomas.

Schiller³ has introduced still another term, "mesonephroma," for malignant ovarian tumors of mesonephric origin. Novak and Woodruff⁴ summarized Schiller's reasoning on mesonephric origin thus: (1) a semblance of the tumor cells to the endothelium of the glomerulus; (2) a generalized tubular pattern histologically resembling the mesonephric tubules; (3) isolated tufts and buds of tumor cells mindful of glomeruli; and (4) a tendency to involve not only the ovary but other areas compatible with a mesonephric origin, such as the broad ligament. They stated in a review of 35 cases of mesonephroma of the ovary from the Ovarian Tumor Registry of the American Gynecological Society that the ovarian tumors formerly spoken of as hypernephroid



Fig. 4. Mesonephroma of the ovary; in one lumen are glomerulus-like protrusions. Glandular spaces are lined with hobnail epithelium.

were actually mesonephric in origin. Stowe⁵ concurs in this view.

In an earlier paper, Novak, Woodruff, and Novak⁶ pointed out that there is a certain group of tumors derived from the Wolffian or mesonephric duct remnants that may arise at any level of the genital tract where the Wolffian duct has previously been present. They have found that the so-called Schiller type of mesonephroma is probably of mesonephric duct origin and is characterized by a glomerulus-like architecture with a tubular pattern featuring a low cuboidal lining epithelium with a frequent peglike budding into the lumen. They believe it is a frequent associate of the clear cell hypernephroid tumor as reported by Saphir and Lackner and that it probably takes origin from the mesonephric duct remnant in the ovary. Novak and Novak⁷ state that their cases show various admixtures of these two tumors, frequently in the same section. Our case, which showed coexistence of a hypernephroid carcinoma¹ and a mesonephroma3 in the same cyst cavity, strongly supports the view held by Novak and co-workers that both types of

tumor have the same origin, i.e., from the Wolffian (mesonephric) duct.

Selye⁸ classified all of these tumors in one category—lipid cell tumors. He states that the possibility that they are morphogenetically heterogenous cannot be excluded but, until better methods are available to determine origin, all may be combined into one group.

From the preceding discussion it becomes readily apparent that at present there is no general agreement on the origin or on the nomenclature of this group of ovarian neoplasms. Yet, they comprise a group of tumors with distinct characteristics histologically related. It is to be hoped that clarification and a standardized nomenclature will soon emerge.

Summary

A detailed case report of a rare disease entity, a hypernephroid carcinoma of the ovary, is presented along with a discussion of the problems of uniformity in classification and terminology of this and related tumors.

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Primary cancer of the ovary

An analysis of 349 cases

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THREE hundred and forty-nine women with previously untreated primary cancer of the ovary have been patients at the Free Hospital for Women from 1904 through 1952. The 238 patients treated before 1943 have been reported in detail by Allan and Hertig. From Jan. 1, 1943, to Dec. 31, 1952, there have been 111 new patients with primary ovarian cancer. Both groups have been combined in a single study, which is presented in this report.

Method

The records of all patients were reviewed and brought up to date as of Jan. 1, 1958, thus giving at least a 5 year follow-up of all cases. Patients lost to follow-up were considered alive only up to the date when last seen or heard from. Only absolute 5 year survival figures are used. We have been able to trace 93 per cent of the patients in the series for at least 5 years. The microscopic sections from the last 111 cases were reviewed and graded in accordance with criteria established by Allan and Hertig1 and used by them in reviewing the sections from the previous cases. The well-differentiated tumors and those thought to represent borderline malignancy were placed in Grade I. The Grade II tumors contained complex epithelial papillae but had little or no solid epithelial growth. Those which had a solid or almost solid histologic growth pattern and contained a high percentage of undifferentiated cells were placed in Grade III. A few tumors were not graded because of unusual and atypical appearance. We have followed the staging classification used in recent papers and originally proposed by Munnell and Taylor²:

Stage I. Cancer limited to one ovary only. Stage II. Cancer limited to both ovaries.

Stage III. Cancer involving other pelvic viscera or pelvic peritoneum.

Stage IV. Cancer involving structures above the pelvis.

Table I shows the incidence of the various types of malignant ovarian tumors encountered in this study, both in relation to each other and to their benign counterparts. Of the total number of 2,530 proliferative ovarian tumors seen at this hospital from 1904 through 1952 the most frequently encountered tumor was the fibroma. There were 739 fibromas but only one fibrosarcoma was found, showing a low malignant potential in this group. By contrast, the serous tumors, composing 24.5 per cent of all tumor types, had the highest malignant potential (34.5 per cent).

Table II indicates the 5 most frequent presenting symptoms and their relative incidence. Pain and distention occurred in over 50 per cent of patients, and abnormal uterine bleeding was noted in over a third. The first two symptoms are typical of cancer of the ovary and may be reasonably ex-

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Table I. Incidence of ovarian tumors

						d malignant
	Be	nign .	Mal	Malignant		% of all
	No.	% of type	No.	% of type	No.	cases
Serous	406	65.5	214	34.5	620	24.5
Pseudomucinous	420	88.0	57	12.0	478	18.9
Unclassified cystadenoma	42	_	-	-	42	1.7
Dermoid cyst	438	98.8	5	1.2	443	17.5
Granulosa cell	29	66.0	15	34.0	44	1.7
Fibroma	739	99.9	1	0.1	740	29.2
Brenner tumor	31	100.0	-	_	31	1.2
Thecoma	56	100.0	_	_	56	2.2
Arrhenoblastoma	1	_	1	_	2	0.1
Miscellaneous benign*	19	100.0	-	***	19	0.8
Undifferentiated carcinoma	_	_	30	-	30	1.5
Mesometanephroma	_	_	9	-	9	0.4
Endometriocarcinoma	_	_	13	_	13	0.5
Dysgerminoma	-		2	_	2	0.1
Carcinosarcoma	_	_	2	-	2	0.1
Total	2,181		349	(13.8)	2,530	100.0

*Includes leiomyoma, adenoma, adenomatoid tumor, adenomyoma, and paraganglioma.

plained on a pathologic basis, but it has often been impossible to explain the abnormal uterine bleeding. It may be that there is an increased production of estrogen as suggested by Hughesdon,³ who has demonstrated the frequent occurrence of luteinized theca cells in the stroma and ovarian mantle of epithelial ovarian tumors.

Table III presents the 5 year survival of patients with symptoms of varying duration. The 5 year salvage in patients with symptoms present for 6 months or over is 42 per cent, while a shorter duration of symptoms is associated with a 34 per cent 5 year salvage. This seems to be true of most internal cancers and probably indicates that the rapidly growing tumors produce symptoms earlier than do those with leisurely growth.

Fig. 1 illustrates the incidence of the 3 categories of tumor by age and the 5 year survival of all patients in each decade. Most apparent is the fact that, with the exception of the second and ninth decades, the serous cystadenocarcinomas predominate in frequency. The serous and pseudomucinous carcinomas maintain a nearly fixed 4 to 1 numerical relationship from 30 through 79 years of age. The other tumor types show a progressively increasing relative incidence through the ninth decade. There is a marked

Table II. Symptoms

Symptom	No. of cases	%
Pain or discomfort	198	56.7
Distention or mass	177	50.7
Abnormal uterine bleeding	120	34.4
Urinary	59	16.9
Gastrointestinal	57	16.3

Table III. Duration of symptoms in relation to prognosis

Duration of symptoms	No. of cases	No. of 5 year survivors	%
Less than 3 months	114	39	34.2
Three to 6 months	80	27	33.8
More than 6 months	135	57	42.2
Total	329*	123	37.4

*In 20 cases the duration of symptoms was not clear.

Table IV. Relation of microscopic classification to grading

	No.	% of cases					
Classification	of	Un- graded	Grade I	Grade II	Grade III		
Serous	214	0	25.7	43.0	31.3		
Pseudomucinous	57	3.5	43.8	45.7	7.1		
Undifferentiated	30	0	3.3	20.0	76.7		
Granulosa cell	15	73.3	0	6.7	20.0		
Total	316	4.1	25.6	39.6	30.6		

Table V. Relation of microscopic classification to staging

	No.	% of cases in each stage					
Classification	of cases	Stage	Stage II	Stage III	Stage IV		
Serous	214	27.1	14.9	22.0	36.0		
Pseudomucinous	57	54.4	3.5	12.3	29.8		
Undifferentiated	30	23.3	10.0	16.7	50.0		
Granulosa cell	15	40.0	13.3	13.3	33.3		
Total	316	32.2	12.3	19.3	36.2		

Table VI. Relation of grading to prognosis

	No. of cases	No. of 5 year survivors	%
Grade I	83	54	65.0
Grade II	131	56	42.7
Grade III	115	12	10.4
Ungraded	20	5	25.0
Total	349	127	36.4

Table VII. Relation of staging to prognosis

	No. of cases	No. of 5 year survivors	%
Stage I	120	64	53.4
Stage II	39	23	59.0
Stage III	70	28	40.0
Stage IV	120	12	10.0
Total	349	127	36.4

drop in 5 year survival after the fourth decade indicating that ovarian cancer is less malignant in young women. The majority of ovarian cancers occur between the ages of 40 and 59.

Grading, staging, and length of survival

Table IV shows the distribution of grade in each of 4 principal tumor types. While 31.3 per cent of serous cystadenocarcinomas were placed in Grade III, only 7.1 per cent of pseudomucinous cystadenocarcinomas were so graded. Most of the granulosa cell and undifferentiated tumors which were graded fell into the Grade III group.

Table V shows the relation of microscopic classification to staging in the 4 principal types. It is interesting that in each type there are more Stage I and IV cases than in the intermediate stages, indicating that, once metastasis takes place, there is a rapid spread above the pelvis or that metastases to both abdomen and pelvis occur simultaneously. The latter would not be surprising in view

Table VIII. Factors affecting prognosis and their relative distribution in the groups treated by operation alone or by operation and x-radiation (327 postoperative survivors)

	Ope	ration (173)	plus	ration x-ray 54)
	No.	% of group	No.	% of group
Grade				
I	43	24.8	35	22.6
II	62	35.8	61	39.6
III	58	33.5	48	31.0
Ungraded	10	5.7	10	6.5
Stage				
I	69	39.3	45	29.2
II	17	9.8	21	13.6
III	32	18.5	36	23.4
IV	55	31.8	52	33.7
Age				
10-19	. 1	0.6	0	0
20-29	7	4.0	7	4.5
30-39	17	9.8	21	13.6
40-49	48	27.8	45	28.6
50-59	44	25.4	49	31.8
60-69	38	22.0	25	16.4
70-79	14	8.1	6	3.9
80 and over	4	2.3	1	0.7
Size				
Not stated	8	4.6	4	2.6
2-5 cm.	5	2.9	21	13.6
5-15 cm.	60	34.6	55	35.6
Over 15 cm.	100	57.0	74	48.0
Consistency				
Not stated	7	4.0	3	1.9
Cystic	72	42.1	63	40.9
Solid	65	37.6	69	45.0
Semisolid	29	16.8	19	12.6
Microscopic type				
Serous	100	57.0	100	65.0
Pseudomucinous	33	19.1	20	13.0
Undifferentiated	16	9.3	12	7.8
Other	24	13.9	22	14.3

Table IX. Relation of grading to radiation response (operative survivors only)

	Grade I		Grade II		Grade III		Ungraded	
	Operation	Operation plus x-ray		Operation plus x-ray		Operation plus x-ray		Operation plus x-ray
No. of cases	43	35	62	61	58	48	10	10
5 year survivors	28	26	24	32	3	9	2	3
% survival	65.2	74.3	38.7	52.4	5.2 (p =	18.8	20.0	30.0

of the intra-abdominal position of many of these large tumors. The difference in malignant potential between serous and pseudomucinous tumors is borne out by this table which shows that 42 per cent of serous tumors and 58 per cent of pseudomucinous tumors had apparently been completely removed by operation. In only 33 per cent of undifferentiated tumors had the disease apparently been completely extirpated.

In Table VI is shown the relation of 5

year survival to grading. Although 65 per cent of patients with Grade I tumors survived 5 years, only 10.4 per cent with Grade III tumors lived that long. The prognostic value of grading is obvious.

Table VII correlates 5 year survival with stage. Although no difference appears between Stages I and II so far as survival is concerned, there is a decreased survival percentage in Stage III and in Stage IV. The impressive figure is the 40 per cent survival

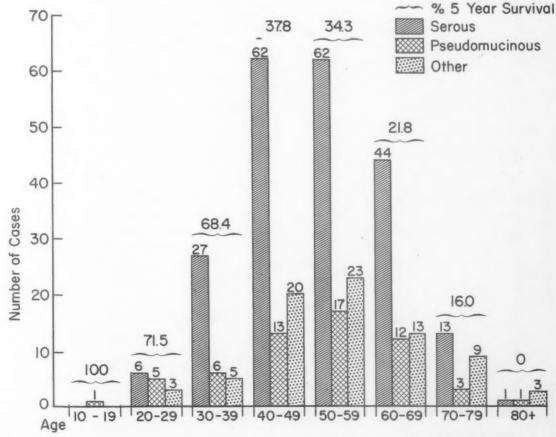


Fig. 1. Age incidence of serous, pseudomucinous, and miscellaneous types, 1904-1952 (349 cases).

Table X. Relation of staging to radiation response (operative survivors only)

	Stage I		Stage II		Stage III		Stage IV	
	Operation	Operation plus x-ray		Operation plus x-ray		Operation plus x-ray	1	Operation plus x-ray
No. of cases	69	45	17	21	32	36	55	52
5 year survivors	32	32	10	13	9	19	6	6
% survival	46.4	71.1	58.8	62.0	28.2	52.8	10.9	11.5
	(p =	.02)						

in patients with Stage III involvement, this probably being accountable to x-radiation delivered to lower abdomen and pelvis.

Radiation response of residual tumor

One hundred and fifty-four patients received immediate postoperative irradiation to the pelvis and lower abdomen as part of their definitive therapy. One hundred and seventy-three patients survived the postoperative period but did not receive radiation. In each case where radiation was used the decision was based on the preference of the patient's physician. Table VIII shows that

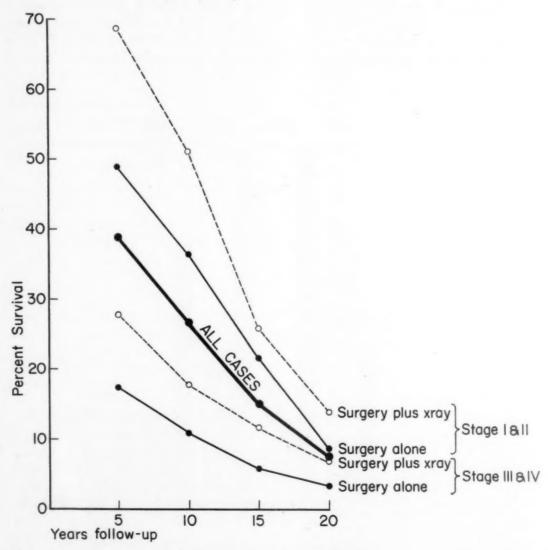


Fig. 2. Long-term follow-up of 327 operative survivors, 1904-1952.

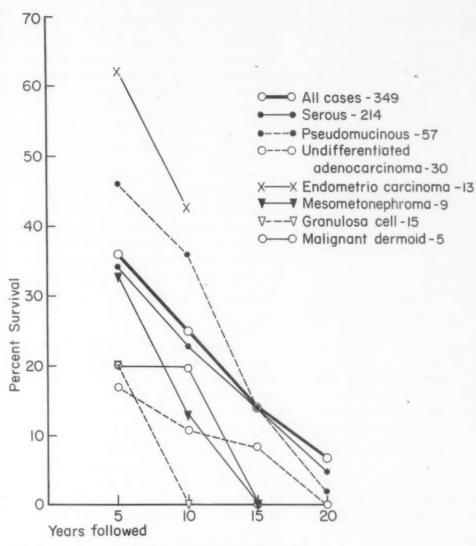


Fig. 3. Survival curves in 7 histologic types, 1904-1952.

the two groups were comparable in every other respect, since the factors affecting prognosis, such as stage, grade, age, and type, were present in each group in approximately equal distribution.

The 5 year salvage rates in the "operation

plus x-ray" and "operation alone" groups, as defined above, were 45.5 per cent and 32.9 per cent, respectively. This difference is significant. Tables IX to XI relate grade, stage, and microscopic type to radiation response. Where differences in survival be-

Table XI. Relation of microscopic type to radiation response (operative survivors only)

	Serous		Pseudomucinous		Undifferentiated carcinoma		Granulosa cell	
	Operation	Operation plus x-ray		Operation plus x-ray		Operation plus x-ray		Operation plus x-ray
No. of cases	101	100	33	20	16	12	5	10
5 year survivors	32	46	16	10	2	5	1	2
% survival	31.6	46.0	48.5	50.0	12.5	41.7	20.0	20.0

Table XII. Relation of treatment to survival

		No.	5 year survivors	% 5 year survival
1.	Biopsy only	23	2	8.7
2.	Biopsy plus x-rays	18	1	5.6
3.	Oophorectomy	45	8	17.8
	Oophorectomy plus x-rays Hysterectomy	18	6	33.3
	and bilateral oophorectomy Hysterectomy, bi-	128	48	37.4 p =
	lateral oophorec- tomy, plus x-rays	117	62	53.0 0.02
De	efinitive proce- dures (5 and 6)	245	110	45.0

tween the two groups are significant by the chi-squared test the "p" values are included in the tables.

Table IX shows the relation of grade to radiation response in all tumors. Although there is some apparent improvement in 5 year survival in all grades with the use of x-ray treatment, the most marked difference is in the Grade III tumors where there is a threefold increase in survival with x-radiation.

Table X presents the radiation response by stage. There is an increase in survival with x-ray treatment in Stage I and Stage III cases while there is no improvement in Stage IV cases. The difference in response between Stage III and Stage IV tumors is reasonable, since tumor is left behind by operation in Stage III tumors and yet it has not extended beyond the scope of pelvic radiation. The difference in survival in Stage I cases cannot be explained on this basis.

Table XI shows the radiation response obtained in 4 principal microscopic tumor types. While serous and undifferentiated cancers show a good radiation response the pseudomucinous and granulosa cell carcinomas do not. This contradicts the experience of others in the case of granulosa cell tumors, but conclusions cannot be drawn from 15 cases. The fact that radiation had no effect on the larger number of pseudomucinous tumors may be more significant.

Treatment

Table XII lists the treatment used along with the 5 year survival obtained in each treatment group. Every patient had exploration and biopsy and, if technically feasible, hysterectomy and bilateral salpingo-oophorectomy. Additional structures, such as omentum, bladder, and bowel, were sometimes resected when involved by tumor. Before 1943 there were few total hysterectomies performed and since then there have been few supracervical hysterectomies. The operative mortality was 6 per cent, mostly in advanced, hopeless situations. The earliest patients in

Table XIII. Extended follow-up on 327 operative survivors

	Stages I and II		Stages III and IV		
	Operation alone	Operation plus x-ray	Operation alone	Operation plus x-ray	All cases
Cases followed 5 years	86	67	87	87	327
5 year survivors	42	46	15	24	127
% survival	48.8	68.7	17.2	27.5	38.8
	(p =	0.003)			
Cases followed 10 years	. 80	45	82	68	275
10 year survivors	27	23	9	12	73
% survival	36.2	51.2	11.0	17.7	26.5
Cases followed 15 years	69	35	68	51	223
15 year survivors	15	9	4	6	34
% survival	21.8	25.7	5.9	11.8	15.2
Cases followed 20 years	61	22	59	30	172
20 year survivors	5	3	2	2	12
% survival	8.2	13.6	3.4	6.7	7.0

this series were apparently treated as aggressively as the more recent patients, since the proportion of patients receiving definitive operations, that is, at least hysterectomy and bilateral salpingo-oophorectomy, has remained around 70 per cent since, as well as before, 1937. Table XII also shows that, with definitive operation alone, the 5 year salvage was 37 per cent. In 117 patients who received definitive operation plus x-radiation the 5 year salvage was 53 per cent.

Conventional x-ray therapy was employed; viz., 200 kv. with 0.5 mm. copper screening and a target distance of 50.0 cm. No patient in this series was exposed above the level of the umbilicus. Portals of entry were 10 by 15 or 15 by 15 cm., both front and back, usually two to the lower quadrants and one to the lower back. The number of exposures varied from 12 to 20. Total doses at the skin level varied from 3,000 to 9,000 r. Dosages delivered to the midpelvic plane varied from 1,400 to 2,600 r.

Twenty year follow-up

In Table XIII are presented the results of the two modes of therapy, operation alone and operation plus x-radiation, in the early (Stages I and II) and late (Stages III and IV) stages of cancer over a 20 year followup period. This is shown graphically in Fig. 2. The increased 5 year survival obtained with postoperative x-radiation is maintained to the 20 year level in both early and late ovarian cancer. The increases shown are significant at the 5 year level in the case of early cancer, but the numbers are not quite sufficient to show this in the late stages. It seems probable, however, that greater numbers would show significance to the 20 year level.

Table XIV and Fig. 3 present a composite 20 year follow-up on 7 microscopic types of ovarian cancer compared with the 20 year survival curve for all cases. The numbers involved are often too small to be of significance, but it is apparent that, with the exception of the endometriocarcinomas, the miscellaneous types of ovarian cancer carry

Table XIV. Extended follow-up on 349 cases by microscopic type

		Cases föllowed	No. survivals	% survival
All cases,	includi	ng postopere	ative deaths	
	years	349	127	36
	years	293	74	25
15	years	238	34	14
20	years	181	12	7
Serous, al	l cases			
	years	214	78	36
	years	193	45	23
15	years	160	22	14
20	years	125	6	5
Pseudomu	cinous			
5	years	57	26	46
	years	55	20	36
	years	50	7	14
	years	43	1	2
Undiffere	ntiated	carcinoma		
	years	30	5	17
	years	28	3	11
	years	23	2	9
	years	16	0	0
Endometr	iocarci	noma		
5	years	13	8	62
	years	7	3	43
	years	5	3	60
	years	3	2 ·	66
Mesometa	inephro	oma		
	years	9	3	33
	years	8	1	13
	years	4	0	0
	years	_	_	-
Granulosa	a cell			
5	years	15	3	20
	years	10	0	0
	years	0	_	-
	years	-	-	-
Malignan	t derm	oid		
5	years	5	1	20
	years	5	1	20
15	years	2	0	0
20	years	-	_	_

a worse prognosis than that of serous and pseudomucinous types.

Summary and conclusions

The clinical and pathologic data from 349 cases of primary ovarian cancer have been presented. An attempt has been made to isolate the important prognostic factors and,

when possible, to study the behavior of the various microscopic types. The effectiveness of postoperative x-radiation has been demonstrated and the situations in which it is most effective have been suggested.

The absolute 5 year survival rate in these 349 patients is 36.4 per cent. Metastases beyond the ovaries were present in 54.4 per cent of these patients at the time of operation.

Grading of tumors microscopically was of value, both in prognosis and in predicting the response to radiation. Stage I and Stage III tumors showed a good response to radiation while Stage IV tumors did not. Pseudomucinous tumors showed no radiation response, while serous and undifferentiated carcinomas responded well.

The best results were obtained when the uterus, ovaries, and as much of the tumor as possible were removed and x-radiation was given postoperatively. The benefits of radiation are maintained to the 20 year level.

We wish to acknowledge the generous assistance of Dr. Malcolm Allan, who provided the material from his paper, and Dr. George V. Smith, who gave serious critical advice and direction.

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Bilateral Brenner tumor of the ovaries

Case report and review of the literature

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ANINTERESTING case of a rare bilateral Brenner tumor stimulated a review of the literature of Brenner tumors in general and bilateral ones in particular. This paper represents a brief summary of the subject.

Mrs. M. Z., a 34-year-old white woman, gravida iii, para ii, who had had one abortion, was first seen by one of us (P. A. B.) in 1956. She was asymptomatic but had been told elsewhere that she might have an ovarian cyst. Her past medical history revealed only a uterine suspension, performed in 1952. Pelvic examination showed a nontender, partially movable cystic mass extending almost across the entire lower abdomen posterior to the uterus. It was felt to be separate from and anterior to the rectum. The patient was hospitalized.

First admission. (Feb. 23, 1956, to March 5, 1956.) An abdominal incision was made. After lysis of extensive adhesions, a cystic mass, 8 cm. in diameter, was found posterior to the uterus originating from the left ovary. In an attempt to excise this cyst, it was entered and 400 c.c. of brownish material was aspirated. The cyst was then found to be quite extensive, extending into the cul-de-sac. Tissue that appeared to be a lymph node was excised from the mesentery of the large bowel. The right ovary and the uterus appeared normal. Nothing further was done at this time. The pathology report revealed "foreign body (suture material) granuloma of fibromuscular and areolar tissue of the mesentery." The postoperative course was uneventful and the patient was discharged on the eighth postoperative day. Pelvic examination later that year showed

no masses, no cystic changes, and no areas of tenderness.

The patient was followed carefully as an outpatient and in September, 1958, she complained of pressure in the vagina. Pelvic examination revealed a cystic mass again in the left adnexal area. Hospitalization was again recommended.

Second admission. (Sept. 28, 1958, to Oct. 26, 1958.) Through an abdominal incision, a cystic mass was palpated in the bony pelvis, involving the left tube and ovary. The right ovary showed a small cystic area. After much tedious dissection associated with considerable bleeding, a total hysterectomy and bilateral salpingo-oophorectomy were performed. During the procedure the cyst was ruptured. The patient's postoperative course was complicated by a *Staphylococcus aureus* wound infection. She was discharged on the twentieth postoperative day.

Pathology report.

Gross description. The uterus measured 8 by 3 by 5 cm. and weighed 100 grams. It was opened anteriorly and the uterine walls measured 1.5 cm. in the region of their greatest thickness. On the anterior aspect of the endometrium was an endometrial polyp measuring 1 by 1 by 1 cm. The remainder of the uterus appeared normal, as did the cervix. No gross evidence of leiomyomas was seen.

Attached to the right side of the fundus in the posterior aspect was the right ovary, which consisted mainly of a small cyst measuring 4 by 2 by 1 cm. Externally, it showed some areas of hemorrhage. Internally, the cyst was smooth and glistening and was yellow-gray in color. Some smaller cystic structures also involved this ovary. The right Fallopian tube appeared normal.

A collapsed cystic structure, measuring 10 by 9 cm., was attached for almost its entire length to the left lateral wall of the uterus in the pos-

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Fig. 1. Left ovary. Nests of epithelial cells surrounded by dense fibrosis. This is the characteristic microscopic picture of Brenner tumors. (Original magnification ×100.)



Fig. 2. Right ovary. Note the central cystic degeneration in the epithelial nest shown, (Original magnification ×100.)

terior aspect. The attachment measured 8 cm. Externally, the cyst was smooth and glistening and pink-gray in color. The internal aspect of the cyst was also smooth. At the superior aspect of this cyst, the left Fallopian tube apparently was included. Near the distal aspect of the tube, some white fibrous and cystic tissue was present.

Microscopic description. The cystic structure of the left ovary was found to represent a serous cyst. In the cyst wall was located a tumor mass composed of sharply delineated rounded nests and columns of squamous-like epithelium, set in a dense fibrous stroma. The epithelial cells were fairly regular in size and polyhedral in shape. The cell borders were distinct. The cytoplasm was light pink, slightly granular, and markedly vacuolated. The nuclei were mostly ovoid with fine dusty chromatin and a small central nucleolus. Occasional grooving of the nuclear membrane was seen (Fig. 1).

In the right ovary, besides the corpus luteum cyst, a group of epithelial nests (as described above) were seen with areas of central cystic degeneration. They were also surrounded by dense fibrosis (Fig. 2).

Final diagnosis. The diagnosis was chronic cervicitis, proliferative endometrium with endometrial polyp, normal myometrium, normal left and right Fallopian tubes, serous cyst and Brenner tumor of the left ovary, and corpus luteum cyst and Brenner tumor of the right ovary.

On the last follow-up visit, the patient was asymptomatic, and pelvic examination revealed a well-healed vaginal vault.

Review of the literature

Although Fritz Brenner¹ is generally given credit for the original description of the tumor which now bears his name, the literature shows that Orthmann² described such a tumor 8 years earlier. Von Mengershausen³ may also have been reporting the same entity. In fact, aside from the latter two authors, at least 7 others may have been referring to this same tumor in their reports. They were Gottschalk,4,5 Amann,6 Macnaughton-Jones,7 Schröder,8 Lönnberg,9 Voigt, 10 and Ingier. 11 All of these men failed to recognize the true nature of this tumor, so a great variety of names were applied. Brenner, himself, called it "oophoroma folliculare"1 because he believed it to arise from the graafian follicle.

Incidence. Peck and Leary¹² state that 2 per cent of all solid tumors of the ovary are Brenner tumors and solid tumors make up 20 per cent of all ovarian growths. Among his 170 cases of Brenner tumors, Fox18 found 13 cases to be bilateral (7.6 per cent). This would make the incidence of bilateral Brenner tumors in all ovarian tumors 0.03 per cent. To Fox's total of 13, one each has been added by Peale,14 Johnson and Dockerty,15 Jondahl, Dockerty, and Randall,16 Peck and Leary,12 Flanagan and Race,17 Rawson and Helman,18 Zhelesnov,19 Zulli,20 de Queiroz,21 and Bungard and Haug.22 This brought the total of bilateral Brenner tumors reported in the world literature to 23. We are reporting the twenty-fourth case.

Although Reagan,²³ in his report on the gross and microscopic pathology of these

tumors, describes 3 cases of bilaterality in his 23 cases, we cannot include them in this survey. His specimens were derived from surgical and autopsy material submitted to his institution "from other sources." Therefore, these cases may have been previously reported elsewhere in the literature and only warrant mentioning here. Reagan also states that statistical incidence of bilateral involvment is unreliable because in many incidences only a single ovary is available for examination.

Summary

The twenty-fourth case of bilateral Brenner tumor is reported. A review of the literature and a discussion of the incidence of this rare occurrence are presented.

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Ovarian dysgerminoma

Report of 8 cases

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THE extremes in management of ovarian dysgerminoma are due to widely divergent attitudes concerning the benignancy or malignancy of the tumor.

It is apparent that confusion pervades the literature to the extent that the individual confronted with managing a case is forced to call on his philosophic rather than on his medical background. This is due to the limited experience in dealing with this tumor. We feel that these facts justify the reporting of 8 cases observed at the City of Memphis and Baptist Memorial Hospitals.

Case 1. A 19-year-old Negro woman, gravida i, para 0, was admitted to the City of Memphis Hospital on Dec. 6, 1956.

This patient was completely asymptomatic; but on a routine initial prenatal visit a mass had been palpated in the abdominal right lower quadrant and right adnexa.

Menarche occurred at age 13 with gradual assumption of a normal menstrual cycle. The patient's last normal menstrual period had occurred Aug. 2, 1956. Pregnancy had been completely uncomplicated up to this time.

The noteworthy physical findings were as follows: The uterus was enlarged compatible with 16 to 17 weeks' gestation, and a 12 to 14 cm. mass was palpable in the right lower quadrant completely filling the right adnexal area.

X-ray examination of the abdomen was negative. Barium enema revealed no evidence of an extrinsic mass.

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Present address: 420 Marquette Bank Bldg., Minneapolis, Minnesota. On Dec. 8, 1956, a pelvic exploratory operation revealed a 15 cm. right ovarian mass which was completely encapsulated with no evidence of extension. The uterus was enlarged compatible with a 16 weeks' gestation. A right salpingo-oophorectomy was done.

The Department of Pathology reported a multilobulated, firm tumor mass, weighing 670.7 grams and measuring 14 by 11 by 7 cm., which on cut section revealed multiple large and small grayish lobulations with fine grayish white septa. Microscopically, the typical picture of dysgerminoma was demonstrated with dense interlacing fibrous connective tissue septa surrounding nests and columns of sharply defined cells with clear cytoplasm and uniformly hyperchromatic slightly bizarre nuclei. This is demonstrated in Fig. 1.

The postoperative period was completely uncomplicated, and on May 4, 1957, after an uneventful pregnancy, the patient was delivered of a 3,543 gram normal female infant.

On Oct. 4, 1957, the patient was readmitted complaining of cramping and vaginal bleeding. She stated that her only menstrual period had occurred on June 12, 1957. Physical findings were those of an incomplete abortion and a dilatation and curettage was carried out. There was no evidence of recurrence of the tumor.

The patient has subsequently been delivered of normal infants on Aug. 20, 1958, and July 29, 1959.

There has been no evidence of recurrence up to this time.

Case 2. A 13-year-old Negro nulligravida was admitted to the City of Memphis Hospital on Nov. 9, 1950, with the chief complaint of an abdominal mass of 2 months' duration associated with minimal lower abdominal discomfort.

Menarche had not yet occurred.

Physical examination revealed an abdominal mass extending from the symphysis pubis to within 3 cm. of the costal margin. Rectal examination confirmed the presence of this mass.

A barium enema revealed the colon to be displaced superiorly by a large abdominal mass. Excretory urography revealed complete obstruction of the right ureter with lateral displacement of the left ureter.

On Nov. 17, 1950, pelvic exploration revealed a 20 cm. mass arising from the left ovary with nodular involvement of the left tube. No other extension of the tumor was noted. A left salpingo-oophorectomy was performed.

The Department of Pathology reported a mass measuring 27 by 17 by 12 cm. which grossly and microscopically fulfilled the criteria for dysgerminoma as previously described. Extension to the left Fallopian tube was demonstrated.

On Dec. 29, 1950, an excretory urogram reported good function in both kidneys but lateral displacement of the left ureter was still noted. At this time the question of metastases to periaortic nodes was seriously considered.

Pelvic examination on Jan. 17, 1951 (2 months postoperatively), revealed no clinical evidence of tumor recurrence. On April 4, 1951, a 6 cm. mass was palpated in the cul-de-sac and was felt to be indicative of a recurrent growth; consequently, x-ray therapy was instituted. Therapy was directed at the pelvis, abdomen, and mediastinum with a 1,500 r tumor dose being administered. No evidence of tumor recurrence has been noted since this therapy.

On Feb. 27, 1957, the patient spontaneously aborted a 24 cm. fetus. On Feb. 14, 1958, she was delivered of a 944 gram infant which died 4 months later of diarrhea, malnutrition, and fluid and electrolyte imbalance; on Dec. 28, 1958, she spontaneously aborted at 20 weeks' gestation.

She remains free of evidence of recurrence of tumor up to this time.

Case 3. This 19-year-old white gravida i, para i, was admitted to the Jackson-Madison County General Hospital in Jackson, Tennessee, on Feb. 26, 1955.

This patient had been delivered normally on Nov. 16, 1954. Pelvic examination 6 weeks later revealed the left ovary to be slightly en-

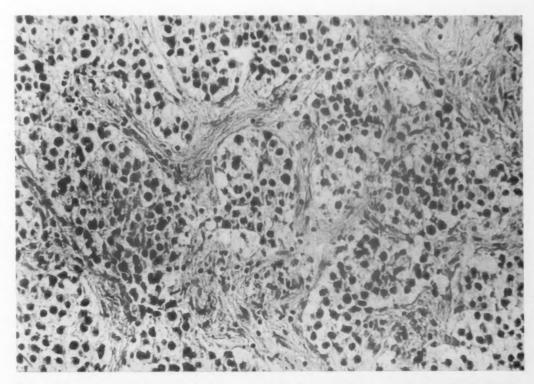


Fig. 1. The typical microscopic findings of dysgerminoma; large, round cells with abundant clear cytoplasm separated by fibrous tissue. (Hematoxylin and eosin. ×10; reduced 1/5.)

larged. In the ensuing 4 weeks a marked increase in the size of the mass occurred.

Past history was completely noncontributory except for the history of a slight menstrual irregularity.

On Feb. 28, 1955, at pelvic exploration, an 18 cm. completely encapsulated adnexal mass was revealed. No additional evidence of extension of the process was demonstrated; therefore, a left salpingo-oophorectomy was performed.

The pathology report showed a 19 by 11 by 6 cm. mass weighing 900 grams which on cut section exhibited lobular areas of whitish, creamy gray material. The typical microscopic features of dysgerminoma were demonstrated.

The patient had a completely uneventful recovery and on July 20, 1955, reported that her last menstrual period had occurred April 19, 1955. At this time the uterus was thought to be enlarged compatible with a 6 to 7 weeks' gestation. The pregnancy was completely uneventful, terminating on Jan. 30, 1956, with delivery of a full-term normal infant.

There has been no evidence of recurrence of the tumor up to the present time.

Case 4. A 26-year-old Negro woman, gravida iv, para iv, was admitted to the City of Memphis Hospital on Oct. 29, 1937, with a chief complaint of menorrhagia of 2 months' duration.

She stated that 2 months before admission she had noted an abdominal right lower quadrant mass which had gradually increased in size.

Menarche had occurred at 13 years of age and the menstrual cycle had remained within normal limits until the onset of menorrhagia. Her youngest child was $3\frac{1}{2}$ years of age.

Physical examination disclosed an abdominal mass approximately the size of a 28 to 30 weeks' gestation. Pelvic examination revealed a normal uterus and left adnexa. There was a mass in the right adnexa confluent with the abdominal tumor.

Laboratory findings were within normal limits except for an abdominal x-ray study which revealed a diffuse, hazy abdominal mass.

On Nov. 26, 1937, pelvic exploration revealed a 10 to 12 cm. right adnexal mass with extension to surrounding bowel and parietal peritoneum. There was approximately 400 c.c. of free fluid in the abdomen. The uterus was three times normal size and the left ovary

seemed uninvolved by tumor. A right salpingooophorectomy was performed with moderate difficulty due to extensive adhesions.

The Department of Pathology reported a 12 by 10 by 6 cm. mass weighing 1,760 grams which presented the typical gross and microscopic characteristics of dysgerminoma.

The patient received postoperative deep x-ray therapy by means of 4 ports and crossfiring the pelvis. Over the period of approximately one month, a total dose of 4,000 r in air was delivered. The tumor dose was not calculated.

Postoperative recovery was complicated by a partial bowel obstruction which responded to conservative therapy.

Return visits revealed no evidence of tumor recurrence. On Nov. 6, 1938 (approximately one year postoperatively), an excretory urogram was reported to be within normal limits and there was no clinical evidence of tumor recurrence. She remains living and well at this time.

Case 5. This 10-year-old Negro child was admitted to the City of Memphis Hospital on Nov. 30, 1949. Approximately one month preceding admission, the patient's mother had noted a mass in the abdominal left lower quadrant which had gradually increased in size. Two weeks prior to admission, the patient had noted slight abdominal aching localized in the left lower quadrant.

On physical examination there was a firm, irregular, nodular mass approximately 12 cm. in diameter located in the abdominal left lower quadrant.

Preoperative excretory urography exhibited a mass obstructing the left ureter.

On Dec. 6, 1949, pelvic exploration revealed a 15 cm. mass arising from the left ovary and intimately adherent to omentum, parietal peritoneum, small bowel, and sigmoid colon. The right ovary did not grossly appear to be invaded by tumor. A total abdominal hysterectomy and bilateral salpingo-oophorectomy was performed after multiple dense adhesions were freed.

The pathology report revealed a mass 15 by 9 by 11 cm. weighing 693.5 grams with gross and microscopic findings characteristic of dysgerminoma.

Over the period of the following week, deep x-ray therapy was administered to the pelvis delivering a total dose of 4,000 r measured in air. The tumor dose was not calculated.

No evidence of recurrence of the tumor was noted until Dec. 8, 1950, at which time the pa-

tient was readmitted with a history of severe intermittent frontal headache of 2 months' duration and continuous headache of 2 weeks' duration. For the preceding 3 to 4 months, marked photophobia had been noted with failing vision for 2 weeks. Total blindness had been present for one week.

On physical examination there was a 5 to 6 cm. mass in the right suprafrontal region, the right pupil was dilated and fixed, and the left pupillary reflex was slightly reactive. There was a total loss of motor function of the left extremities.

X-ray examination of the skull demonstrated destruction of both the inner and outer skull tables with evidence of increased intracranial pressure.

The patient died 62 hours after admission. At necropsy, widespread metastatic dysgerminoma was observed.

Case 6. A 7-year-old Negro child was admitted to the City of Memphis Hospital on June 29, 1943. Progressive enlargement of the child's abdomen had been noted by the mother over a period of 3 weeks. Anorexia and urinary frequency had been present for one week.

On physical examination massive ascites was demonstrated with a large mass filling the entire abdomen. Bilaterally enlarged supraclavicular nodes were palpated.

Laboratory results disclosed profound anemia (red blood count 2.3 million and hemoglobin 7 Gm.). X-ray examination of the abdomen revealed a huge mass with bilateral elevation of the diaphragm, and a soft tissue density was noted at the base of the right lung.

On July 12, 1943, an exploratory laparotomy revealed (1) serosanguineous ascites, (2) right ovarian mass 18 to 20 cm. in diameter, (3) metastatic lesions over the inferior surface of both leaves of the diaphragm, and (4) massive anterior peritoneal metastatic implants. The right ovarian mass and an implant on the diaphragm were biopsied and the pathologist reported dysgerminoma.

The patient died 17 days after admission (3 days postoperatively). At necropsy the right ovarian tumor was found to weigh 800 grams and measured 16 by 12 by 11 cm. The tumor had invaded the omentum, parietal peritoneum, and rectosigmoid, with metastatic involvement of the diaphragm, retroperitoneal, anterior and posterior mediastinal, left axillary, and right

cervical lymph glands. The gross and microscopic picture was that of dysgerminoma.

Case 7. A 14-year-old Negro girl was admitted to the City of Memphis Hospital on April 20, 1959, with a chief complaint of rapid enlargement of the abdomen of 2 weeks' duration and lower abdominal pain of 8 days' duration.

Menarche had occurred at 12 years of age and the patient stated that she had a normal menstrual cycle.

On physical examination an 8 to 10 cm. abdominal mass was palpated to the right of the umbilicus. The liver extended 6 to 7 fingerbreadths below the costal margin. On pelvic examination, bilateral cystic adnexal masses were palpated.

X-ray studies were reported as follows: chest, negative; barium enema, an extrinsic mass narrowing the sigmoid with small bowel compressed into the upper abdomen; excretory urogram, extraurinary mass compressing the right ureter.

On May 5, 1959, pelvic exploration established the presence of a 15 by 20 cm. mass arising from the right ovary with direct extension to the omentum and peritoneum. A 10 by 15 cm. mass arose from the left ovary with extension to the urinary bladder, uterus, left tube, colon, and peritoneum. There was no involvement of the liver. The entire tumor mass was intimately adherent over the iliac arteries. An attempt was made to resect as much tumor as possible but complete removal was deemed inadvisable because of the intimate vascular involvement. A bilateral salpingo-oophorectomy was performed. The gross and microscopic findings were those of dysgerminoma.

Over the period of the next 48 days the patient received deep x-ray therapy as follows: 2,000 r to the abdomen, 2,000 r to the pelvis, and 564 r to the chest.

This patient has been re-examined at monthly intervals and remains free from evidence of tumor recurrence. Excretory urography has demonstrated no evidence of ureteral compression.

Case 8. A 33-year-old white gravida 0, para 0 was admitted to the Baptist Memorial Hospital on Nov. 26, 1958, complaining of lower abdominal pain and an increasingly perceptible mass of 4 months' duration.

In January, 1955, during a routine pelvic examination elsewhere, a 6 to 7 cm. right adnexal mass was palpated. Surgical exploration revealed dysgerminoma of the right ovary with-

out gross evidence of tumor extension. A right salpingo-oophorectomy was performed. She remained asymptomatic without evidence of recurrence until the time the above symptoms were noted.

The patient's past history disclosed primary amenorrhea. She stated that she had never had a menstrual period and her previous physician had explained that her "female organs had never developed."

On physical examination an ectomorphic body habitus was observed. A large abdominal mass was palpated extending from the symphysis pubis to within 3 fingerbreadths of the costal margin. Moderate enlargement of the clitoris was present and the vagina would not admit an infant-sized speculum. On rectal examination the uterus could not be delineated from the large abdominopelvic mass. Preoperative excretory urography demonstrated obstruction of the right ureter.

On Dec. 1, 1958, abdominal exploration revealed a large lobulated tumor extending from the right lower quadrant to the subhepatic area. The mass was intimately adherent to both large and small bowel, parietal peritoneum both anteriorly and posteriorly, and the lower portion of the abdominal aorta. Surgical removal was deemed impossible; therefore, a portion of the mass was excised for biopsy. The Department of Pathology reported typical dysgerminoma in this tissue.

Over the period of the next 30 days the patient received external radiation administered from a cobalt teletherapy source.

In the ensuing 3 months a rapid disappearance of the abdominal tumor mass was observed. On Aug. 12, 1959, the mass could no longer be palpated and excretory urography revealed normal kidney function bilaterally. There was no radiological evidence of tumor recurrence.

Comment

Dysgerminoma is a rare tumor making up approximately 3 per cent of all primary ovarian malignant tumors according to Fauvet² (quoted by Novak¹⁰). This is further evidenced by isolated case reports expressing divergent views concerning management of the individual patient suffering from this tumor. To demonstrate this enigma, a copy of the history, surgical, and

pathological findings of Case 3 was sent to the professors of obstetrics and gynecology of 9 medical schools throughout the United States. Their opinions as to management of the case were as follows: 3 recommended no further treatment other than close observation; 4 recommended immediate reoperation with removal of the uterus, remaining tube, and ovary; 2 recommended intensive deep radiation therapy.

In reviewing the literature, Mueller and associates⁶ and Pedowitz and co-workers¹¹ ascribe a mortality rate in the order of 72 per cent to this tumor. In the group of patients herein studied, the mortality rate was 25 per cent. Admittedly, 2 patients are still in their first year after therapy; therefore, true 5 year survival cannot be calculated.

Pedowitz and co-authors11 stated that fewer deaths result from dysgerminoma in the 15 to 40 year age group than in older or younger patients. Four patients in this series were below the age of 15. Two are dead and 2 are living and well; therefore, we can neither agree nor disagree with his figures. This tumor, like so many others involving the ovary, in its early stage is completely localized. With this fact in mind, it becomes obvious that earlier intervention should result in a vastly improved prognosis. The entire group of patients in the age span to which the majority of the lay literature concerning early diagnosis and treatment of cancer is directed are in the group surviving this tumor. The problem now resolves itself into two facets: (1) additional lay publicity bringing to the attention of parents the seriousness of tumors in children, and (2) definitive diagnosis and adequate therapy in these younger individuals before extension of the localized tumor

It has been conjectured that the seemingly different degrees of malignancy may be based upon some as yet unrecognized component of dysgerminoma. Neigus reported a case of dysgerminoma associated with chorionepithelioma. The coexistence of totally unrelated lesions is not unique in the annals of medicine. If Meyer's postulates on

histogenesis are correct, it is safe to assume that various exotic lesions might appear by happenstance in an ovary involved by dysgerminoma.

In considering the actual therapy of the patient, we are of the opinion that, given a completely circumscribed lesion with no gross evidence of local extension which would be demonstrated by adherence of omentum, bowel or peritoneum, enlarged retroperitoneal nodes, or involvement of the contralateral ovary, unilateral oophorectomy is sufficient. This is dependent upon the patient's desire for preservation of the child-bearing function.

All solid tumors of the ovary should be subjected to intense scrutiny by both the surgeon and the pathologist at the time of operation. Dockerty and MacCarty1 call our attention to 2 gross and 2 microscopic features which characterize this tumor. Grossly these neoplasms are nearly all of a peculiar brainlike consistency with broad zones of necrosis and hemorrhage. Microscopically the stromal reaction with lymphocytes, foreign body giant cells, and large, round tumor cells are almost pathognomonic. If both the surgeon and the pathologist bear this description in mind, definitive therapy can be carried out at one sitting rather than having the patient subjected to a second laparotomy several days later.

Given evidence of extension, the surgical procedure should be of a more radical nature, irregardless of the age of the patient. This would be in the form of a total abdominal hysterectomy and bilateral salpingo-oophorectomy. We feel that the patient in whom extension of tumor beyond the limits of operation has occurred should receive radiotherapy as soon as feasible postoperatively. The radiosensitivity of this tumor is well recognized and the recommendation of withholding therapy until clinical evidence of recurrence is demonstrated will continue to result in the high mortality rate from this tumor.

It is recommended that when radiotherapy is administered, it be directed to the entire pelvis and retroperitoneal nodal area. With

this manner of treatment, the entire area of potential nodal involvement is treated. In the extremely young age group sufficient radiation should be administered to guarantee cessation of ovarian function. In Case 2 radiotherapy was administered after evidence of metastasis was found. This patient became pregnant 6 years later and aborted. One year later, she was delivered of a premature infant. This points out that in order to suppress ovarian function in these young individuals, an extremely high dose of radiotherapy must be given. In this day and age of concern over short- and long-term effects of radiation, we must be absolutely certain of the prevention of future childbearing in these individuals so intensively treated radiologically.

The value of excretory urography in evaluating the degree of spread of the tumor is well demonstrated in 4 of the cases herein described. Its use, when coupled with operative findings, will render invaluable information in selecting patients for post-operative radiotherapy.

In this series, one patient was noted to have underdeveloped genitals and it is highly possible that she may be classified into the general group of pseudohermaphroditic individuals. The chromosomal pattern of cells obtained from the buccal mucosa would be of aid in definitely determining the presence or absence of this entity. Reference is made repeatedly to the incidence of pseudohermaphroditism coexisting with this tumor.3-5 The fact that many of these tumors are discovered in pregnancy points out that pseudohermaphroditism per se is either merely a coincidental finding or the progenitor of pseudohermaphroditic changes and dysgerminoma are one and the same. In his original paper, Meyer⁵ reported 27 cases of associated pseudohermaphroditism and dysgerminoma, but other papers have not substantiated such a high incidence.8,9 It must be recognized that the pseudohermaphrodite with a dysgerminoma will still exhibit the genital abnormality after removal of the tumor.

Summary and conclusions

1. Eight cases of dysgerminoma of the ovary have been presented with complete case reports of each. Four of these cases occurred in girls less than 15 years of age.

2. The gross and microscopic criteria have been presented. They consist grossly of lobulation and a brainlike consistency with the microscopic picture demonstrating large, dark tumor cells in a fibrous tissue framework.

3. Local or distant metastases should be treated radically by a combination of excision and intensive deep radiotherapy in all patients irregardless of age.

We wish to express our deep appreciation to Dr. Arnold Truex, Jackson, Tennessee, for his permission to include one of the above cases in this report.

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Stromal "endometriosis" with possible ovarian origin

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STROMAL endometriosis, also variously known as stromatous endometriosis, stromatosis, and stromal adenomyosis, has been recognized and described as an entity for many years, 1, 3, 4, 5, 10, 12, 13 but there is still uncertainty as to its histogenesis, prognosis, and relationship, if any, to endometriosis and endometrial sarcoma.

About 100 cases of stromal endometriosis have been reported in the English literature.12 The condition is probably more common than this would indicate because of its confusion with certain cases of endometrial sarcoma.13 Novak8 maintains that the histologically malignant type should be regarded not as stromatosis but as one variety of endometrial sarcoma, yet it is generally accepted that even the histologically benign types may occur beyond the confines of the uterus and even occasionally cause distant metastases.4 The majority of the reported cases were in women between the ages of 30 and 50 years of age, and at least 8 occurred after the menopause; the latter fact, and the experience that the lesion does not usually disappear after oophorectomy, would show that (unlike endometriosis) its activity does not depend on the ovarian hormones.4 Most authors believe11 that stromatosis is merely a variant of uterine adenomyosis, and all are agreed¹² that the lesion originates in the stromal cells of the uterine endometrium. The relationship of the condition to endometriosis is, however, not so clear, although several patients have been found to have both lesions. The prognosis, while uncertain, is generally good when the lesion is adequately removed, but in some cases recurrences have occurred many years later.⁴ The tumor is often remarkably sensitive to irradiation, but the regression is usually only temporary.^{2, 6}

The case to be described here presented remarkable features, some of which have apparently not been reported before. The outstanding feature was that, quite contrary to the generally accepted uterine origin of stromatosis, the ectopic stromatous tissue suggested an ovarian etiology more strongly than an endometrial one. True endometriosis of a more marked degree than we have previously seen was also present in the rectovaginal septum, and again there was massive invasion of the omentum by the stromatous tissue. Yet the short-term result of treatment has been encouraging and. contrary to the usual experience, the lesion appears to be regressing following removal of the ovaries.

Case report

L. J., a 37-year-old Negro woman, was seen at the gynecological outpatient department of the Groote Schuur Hospital, Cape Town, on June 2, 1959. Her only complaint was that of

From the Department of Gynaecology and Obstetrics and the Department of Pathology, University of Cape Town/Cape Provincial Administration. continual, daily vaginal bleeding of 4 months' duration. There was no alteration in the menstrual cycle, which had remained regular, with menses occurring every 28 days and lasting 3 to 4 days, since the menarche at the age of 12 years; the last menstrual period had been on May 18, 1959. She had no pain, dyspareunia, or bladder or bowel disturbances, her weight remained stationary, and her general health good. She had had 6 full-term normal deliveries; the youngest child was born 1 year previously.

On examination she looked remarkably well. Her blood pressure and urine were normal; the hemoglobin level was 11 Gm. per cent. A hard, mobile gland about 3 cm. in diameter was palpable in the right groin but the abdomen was clinically normal. A large firm indurated craggy mass was felt in the rectovaginal septum, measuring about 7 cm. in length, 4 cm. in width, and 2 cm. in thickness; it was attached to the mucous membrane of the anterior vaginal wall in 3 areas, where purple nodules were seen. The mass was completely nontender and on rectal examination it was not adherent to the rectal mucous membrane. The right uterosacral ligament was thickened. The uterus was not enlarged, but its mobility was impaired; the right ovary was not palpable. Proctoscopic and sigmoidoscopic examinations revealed no rectal pathological conditions and all x-ray investigations were negative, including those of the chest and intravenous pyelogram and barium enema.

On June 6 (i.e., on the twenty-fourth day of the menstrual cycle) a curettage was performed and two biopsy specimens were taken from the rectovaginal mass. Histological examination confirmed the presence of endometriosis in the rectovaginal septum; the ectopic endometrial glands were in the proliferative phase of the cycle, while the curettings showed a secretory phase (see pathological description and Fig. 1).

On June 18 a laparotomy was performed. The uterus was slightly enlarged and was fixed by surrounding adhesions; the left ovary was enlarged and the right one more so, being the seat of a chocolate cyst. The omentum was markedly thickened and appeared to be heavily infiltrated by "growth"; there were also many large glands about the size of grapes, as well as smaller ones, along the external and internal iliac vessels and the aorta. The picture at operation was one of inoperable malignant disease. No primary lesion could, however, be felt in the gastrointestinal tract. In order to obtain histological data, and in

the hope that the lesion may have been one of endometriosis, both ovaries, as well as the omentum, were removed.

The patient made an uneventful recovery and when seen 5 weeks later her general condition was excellent. The gland in the right groin had disappeared and the large mass in the rectovaginal septum was no longer palpable.

Pathology. The uterine curettings showed premenstrual secretory phase endometrium. The biopsies from the rectovaginal mass presented the features of typical endometriosis (Fig. 1); glands were plentiful but neither the glands nor the stroma showed the changes which were present in the curettings from the uterus.

The laparotomy specimen consisted of left and right ovaries and a mass of very bulky omental tissue 13 cm. long, showing tough yellow and gray tissue replacing most of its normal fibroadipose structure. The right ovary was 6 cm. in diameter and was attached to an apparently normal Fallopian tube 4 cm. long; the ovary when sectioned showed a chocolate cyst, a corpus luteum, and some irregularly shaped dull yellow and gray areas. The left ovary was also attached to a normal Fallopian tube and was 41/2 cm. in its greatest diameter; it showed on the cut surface a small corpus luteum and several separate dull yellow areas up to 1 cm. in diameter. The corpus luteum and endometriosis with cyst formation were confirmed in sections from the right ovary. Glands of endometrial type were scanty in the endometriosis, and the stroma immediately suggested an ovarian and not an endometrial origin. The stroma consisted of spindle-shaped cells irregularly subdivided by well-formed small blood vessels; the bulk of the stromal cells were plump and closely packed, but others were thinner and looked very much like fibrocytes. Histological sections from the left ovary showed the same microscopical features but the stroma in this ovary was not accompanied by endometrial glands. The appearances in both ovaries were indistinguishable from those of diffuse theca cell hyperplasia. The same type of tissue was, however, widely distributed throughout several sections from the omentum (Figs. 2 and 3), and each focus of spindle-shaped cells was so well differentiated that it resembled mature and ripening ovarian stroma forming fibrous tissue. Collagen fiber formation by some cells was indeed demonstrated, though scanty. There was a relative absence of mitotic activity.



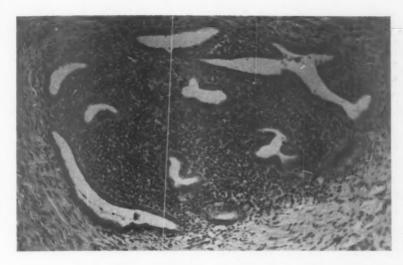


Fig. 1. Endometriosis in rectovaginal septum.

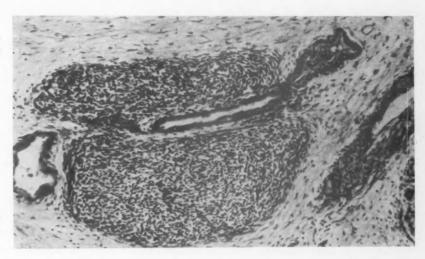


Fig. 2. Perivascular stromatous focus in omentum.

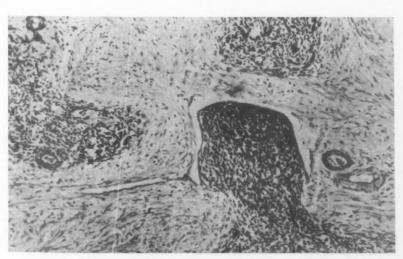


Fig. 3. Stromatous tissue apparently in preformed omental space.

Comment

The case presented several remarkable

There was both endometriosis and stromatosis, each lesion being extensive, although in different situations. This association has been described by others.5, 6 Endometriosis was present in the rectovaginal septum and in a portion of one ovary, while there was stromatosis in both.

The omentum and, probably, lymph nodes were massively infiltrated by stromatosis. Such involvement has only very rarely been reported.4, 10

The most striking feature of the case, and a finding that has apparently not been reported before, was the strong evidence for an ovarian origin of the stromatosis rather than an endometrial one. The appearance in both ovaries was so indistinguishable from that of diffuse theca cell hyperplasia that such a diagnosis would certainly have been made had ovarian tissue alone been available for study. The wide distribution of the same type of tissue throughout the omentum suggested the possibility of sarcoma. However, it is almost unknown for a thecoma to metastasize, and the histological appearance of the uterine curettings indicated an absence of excess estrogen secretion. The bulk of the histological evidence was also against such a diagnosis. Each focus of cells was so well differentiated that it resembled mature ovarian stroma, and scanty collagen fiber formation was actually demonstrated. However, this was so scanty that it could not be taken as proving the ovarian origin of the metastatic tissue.

A benign process was also suggested by the absence of excessive mitotic activity or necrosis in the omental foci and the fact that where the normal and "neoplastic" tissue met there was no destruction or even compression of the normal. Intravascular stromal tissue was also not demonstrable, although the masses of cells were predominantly perivascular in distribution and occasionally even made their way into clefts lined by flattened cells. The tissue, therefore, seemed to lack all neoplastic feature except metastasis; even this property occurred in the rather loose and descriptive sense that is applied to endometriosis.

Stromal endometriosis, in which stroma without glands is found in abnormal sites. seemed to offer a reasonable explanation for the pathological findings. The substitution of ovarian for endomentrial stroma, although apparently not previously described, would seem quite acceptable, in view of the fact that endometriosis has its origin from "abnormal differentiation in the coelomic epithelium," from which all the genital epithelium of the ovary arises.7,9 Such differentiation may occur as the result of a hormonal or other stimulus and might lead to the appearance of glands in some ectopic foci and stroma in others, as was demonstrated in this case.

It is difficult to assess the prognosis of this case. The published case histories of patients with stromal endometriosis suggest a more hopeful outlook than in those with endometrial sarcoma. It is well known that the elimination of ovarian function by operation or irradiation will cure endometriosis, but the relatively scanty evidence available suggests that this does not necessarily apply to stromatosis. Cases can develop after the menopause, and the condition has recurred after total hysterectomy and bilateral salpingo-oophorectomy.

The disappearance of the endometriosis in the rectovaginal septum in this case following the extirpation of the ovaries was not surprising, but the complete shrinkage of the gland in the groin was a somewhat unexpected, though hopeful, sign. The enlargement of this gland and, presumably, the periaortic ones may well have been due to stromatosis but, since histological examination of these nodes was not carried out, it is realized that endometriosis or reactive changes may have been responsible. The different origin of the stromal tissue may also mean a different prognosis. The patient is being observed at frequent intervals but the prognosis must remain in doubt for some time to come.

Summary and conclusions

- 1. A case is reported with features conforming to stromal endometriosis in a 37-vear-old woman.
- 2. An unusual feature was the extension of the tumor to the omentum and possibly to periaortic lymph nodes.
- 3. Unlike other cases in the literature, the histological features suggested an ovarian and not an endometrial origin.
- 4. The short-term prognosis has been very good, but the long-term outlook is a matter for speculation.

We would like to thank J. T. Louw, professor of Obstetrics and Gynaecology, University of Cape Town, and J. G. Thompson, professor of Pathology, University of Cape Town, for advice and helpful suggestions. The patient was under the care of Dr. P. Massey at the Groote Schuur Hospital, Cape Town, and Dr. A. Michael carried out the operative treatment; we are grateful to them for allowing us to examine the patient, follow her progress, study the pathology, and publish the report.

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Testicular feminizing syndrome in male pseudohermaphroditism

A report of its occurrence in successive siblings

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THE intersexual patient or the patient who is diagnosed as being either a true hermaphrodite or a pseudohermaphrodite presents a problem not only to the physician but also to herself. By definition, the true hermaphrodite must have gonads of both sexes; only 75 cases have been reported.1, 2 "Pseudohermaphrodite" is a term formerly applied to the adrenogenital syndrome in the female with the gonads of one sex (female) and the external genitals of the other sex (male). One of the syndromes also often called pseudohermaphroditism is the testicular feminizing syndrome. This particular syndrome is one that is not conducive to early diagnosis as the patient presents all the outward manifestations of a "normal female." The following characteristics usually are shared by those who possess this syndrome3:

- Female habitus with normal female fat deposits. Long extremities and long hands and feet may or may not be present.
- 2. Normal female breasts. The breasts may even be overdeveloped although the nipples are sometimes juvenile.
- 3. Absent or scanty axillary and pubic hair. There may or may not be vulvar hair. The hair on the head is of a normal female

distribution and no recession of the hairline is seen. Facial hair is absent.

- 4. Female external genitals are present. The labia may be underdeveloped, especially the labia minora, and the clitoris is small or normal in size. The vagina ends blindly but is adequate for coitus.
- 5. The internal female organs are rudimentary or absent, and the gonads are either intra-abdominal or in the inguinal canal.
- 6. The gonads are undescended testes. They contain mostly seminiferous tubules usually without spermatogenesis. An increased number of interstitial cells are usually present. The microscopic appearance of the gonad is similar to the cryptorchid testis. Tubular adenomas are not uncommon.
- 7. Hormone assays indicate normal or near normal levels for estrogens and androgens. Pituitary gonadotropins have been elevated in some cases.
- 8. A strong familial tendency is seen in this syndrome as indicated by the proportionately large number of cases in "sisters and aunts" that have been reported in the literature.

Case reports

The following 2 case histories are in successive siblings, aged 16 and 17 years, respectively:

Case 1. A. S., a 17-year-old white girl, presented with the chief complaint of spotting of several months' duration. The history indicated

From McDowell Memorial Hospital.

*Present address: Department of Obstetrics and Gynecology, Western Reserve University School of Medicine, Cleveland, Ohio. a gradual onset of secondary sexual characteristics at age 12 characterized by enlargement of the breasts and some slight growth of pubic hair. The main concern was the mother's anxiety because of the patient's amenorrhea. The patient had seen another physician and was treated with hormone injections without benefit. She was referred by him for the care of a urethral caruncle which was the cause of the spotting and which resulted in some lower urinary tract irritative symptoms.

The past history was not remarkable. Family history showed a sibling aged 16 also had amenorrhea. An older sister was married and had 3 children. This older sister and the mother both had had an uneventful menarche at age 12. The mother stated all of her pregnancies were normal. No difficulty was encountered with the prenatal period, except for mumps in the first trimester when she was pregnant with Patient A. S.

Review of systems was negative. The patient was a junior in high school and apparently had developed normally.

Physical examination. The patient appeared to be a normal adolescent girl with normal female fat distribution and average developed

breasts and nipples. She was of average height (66 inches) and weight (130 pounds). There was scant hair in the axilla and some hair in the pubic region which appeared to resemble a male type distribution. The remainder of the general examination was negative.

Pelvic examination. There was a 2 cm. papillomatous growth arising from the external urethral orifice. The external genitals appeared to be normal except for a lack of pigmentation of the labia. The vaginal mucous membrane was a healthy pink color and gave the appearance of adequate estrogenation. The vagina was of normal length but ended blindly, and no cervix was present. A 6 cm. adnexal mass was present on the left. The right adnexa were normal to palpation, but the uterus could not be outlined. A tentative diagnosis was made of: (1) urethral caruncle and (2) developmental defects of the pelvic organs.

Case 2. L. S., the younger sister, aged 16, also had amenorrhea and presented the same clinical picture except that the adnexal mass and urethral caruncle were not present.

Baseline laboratory studies were carried out on both patients and included two intravenous pyelograms, both of which were negative. The

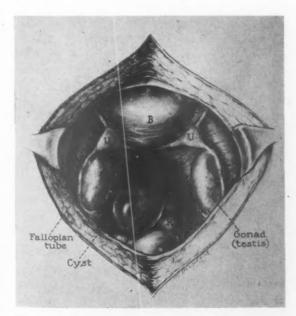


Fig. 1. Pelvic contents of A. S. (aged 17). B, Bladder; U, uterus; R, rectum, gonad (testis), Fallopian tubes, and cyst (hydatid of Morgagni). Note origin of round ligaments arising from the uterus and band of tissue extending from apex of vagina to both "uteri."

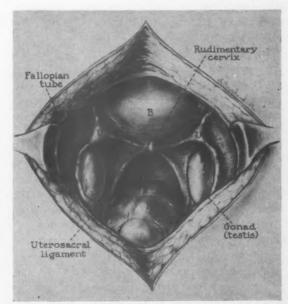


Fig. 2. Pelvic contents of L. S. (aged 16). B, Bladder; U, uterus; R, rectum, gonad (testis), Fallopian tubes, uterosacral ligaments, and rudimentary cervix. Note presence of rudimentary cervix and attached uterosacral ligaments that were absent in Fig. 1.



Fig. 3. Gonad (testis). (×140; reduced 1/5.)

first patient (A. S.) was O negative, whereas the second (L. S.) was O positive. 17-Ketosteroid determinations on both patients preoperatively were within normal limits (A. S., 6.84 mg.; L. S., 7.4 mg.).

Surgical findings. Patient A. S. was taken to the operating room for an examination under anesthesia and for excision of the urethral caruncle. The above findings were confirmed and it was felt that the patient did not have a uterus.

An exploratory laparotomy was performed on the older sibling (A. S.) and the following was found (Fig. 1): (1) a band of tissue extended from the apex of the vagina laterally to both pelvic walls where (2) a presumed uterus was located as characterized by a condensation of fibrous tissue measuring 1 by 3 by 2.0 cm.; (3) a ligamentous structure presumed to be the round ligament arose from one pole of the "uterus" and entered the inguinal canal; (4) a structure resembling a rudimentary tube with fimbria arose from the other pole of the "uterus" and coursed over the gonads; (5) the gonads were in the location of normal ovaries and possessed a thick white capsule; they measured approximately 1.5 by 1.0 by 3.0 cm.; (6) there was a 6 cm. cystic structure arising adjacent to the left gonad which was presumed to be a hydatid of Morgagni.

Upon abdominal exploration, L. S. had similar findings with the following exceptions (Fig. 2): (1) a condensation of tissue was present in the midline at the apex of the vagina that measured 1.5 by 1.0 cm. and was presumed to be a rudimentary cervix; (2) arising from this were prominent sacrouterine ligaments which were absent in the other sibling.

The operations performed on both patients consisted of wedge resections of both gonads; biopsy specimens were taken of all structures even though they appeared to be identical in appearance and were bilateral. Incidental appendectomies were also performed.

The pathology reports on the tissue submitted revealed the gonads of both patients to be testicles (Figs. 3 and 4); the presumed uteri contained only fibromuscular tissue with no endometrium, and the rudimentary tubes contained tubal epithelium (Fig. 5).

Vaginal smears and blood smears failed to reveal any evidence of female nuclear sex chromatin patterns in either patient. The vaginal smears appeared to indicate adequate estrogen stimulation. Gonadotropin assays were within the range of normal (A. S., less than 8 mouse units; L. S., greater than 12 but less than 24 mouse units). Repeat 17-ketosteroid determinations 18 months later were unchanged for A. S. (8.8 mg.) but were elevated for L. S. (24.6 mg.).

It was elected to follow these patients without therapy and at the present time 2 years have elapsed since operation with no appreciable change in their status.

Comment

The mechanism of development of these intersexual individuals is unknown. Greene⁴ doubts that any one theory can explain the mechanism of development in cases of intersexuality. This is probably true since many individuals are categorized as pseudohermaphrodites and possess a gamut of developmental defects. The testicular feminizing syndrome is reasonably consistent in its developmental defects and has certain common denominators; the following generalizations are applicable: there is a male nuclear sex chromatin pattern, the gonads are testes, and these individuals appear to be "normal"

females." Recent evidence by Ford and associates5, 6 and Fraccaro and co-workers7 has brought forth new data concerning the chromosomal patterns in Turner's and Kleinfelter's syndromes, and this raises the question as to whether this syndrome is similar. Probably there is no similarity of the chromosomal patterns because of the mode of transmission. Taillard and Prader8 discussed 10 families in which individuals were known to exhibit the testicular feminizing syndrome. They postulated the genetic explanation was on the basis of inconstant nondisjunction of the X chromosomes. Steinberg,9 in reviewing this article, felt these conclusions were erroneous and the genetics of this syndrome were best explained as recessive sex-linked inheritance with the trait being carried by the X chromosome. This interpretation fitted the data for these 10 families.

The genetic balance between male determiners and female determiners reaches its greatest impact upon the bipotential gonad at the end of the second month of embryonic development, resulting in the de-

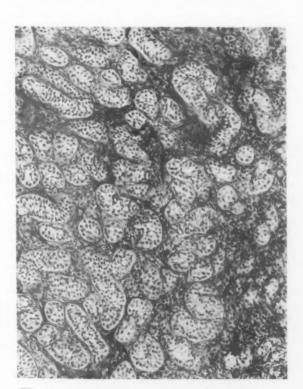


Fig. 4. Gonad (testis). (×504; reduced 1/5.)



Fig. 5. Cross-section of Fallopian tube. (×30; reduced 1/5.)

finitive development of either an ovary or testes. A defect in the production of the masculinizing evocator by interstitial cells of the testes, which has a local action on adjacent tissues, probably is responsible for failure of male development in the reproductive system away from the gonad.10 This evocator may be similar to the antitestis factor described by Segal and Nelson.11 This syndrome strengthens the evidence that ovaries are not essential for female development. The absence of ovaries or the lack of adequate masculinizing evocator probably accounts for the incomplete development of the Müllerian duct system in the testicular feminizing syndrome.

The next major impact on these individuals is puberty when the gonad begins to produce both estrogen and androgen. The previously present but undeveloped female structures then respond in varying degrees to the estrogen production of the testis.

Fellner¹² first observed that lipoid extracts of bull testis produced an estrogenic response. There is unanimity of opinion that

the sustentacular cells of Sertoli are the source of estrogen in the testis. 13-16 This source of estrogen is apparently enough to result in either complete or incomplete secondary sexual development.

A reasonable amount of concern is entertained about the gonads in these patients after puberty. The major consideration is the potential development of malignant changes or adenomatous changes. The opinion is somewhat divided as to the urgency of castration2, 3, 17, 18; however, it seems well established that these gonads are more predisposed to malignant changes than normally located testes.

The problems of management in these cases are reasonably well agreed upon and are as follows2, 3:

- 1. A diagnosis must be established. It is usually necessary to perform an exploratory laparotomy for a definitive diagnosis. The gonads and rudimentary structures should be biopsied. Appropriate endocrine studies and sex chromosomal pattern determinations may be helpful.
- 2. Renal anomalies do not seem to occur as frequently in this syndrome as in other developmental defects of the female genital tract, but a minimum work-up should include an intravenous pyelogram.
- 3. Once a definitive diagnosis has been established a decision must be made as to whether or not the gonads should be removed. If the patient is past puberty, one of the favoring evidences for castration is

the malignant potential of the gonads. If castration is carried out, supplemental estrogen therapy is mandatory for the remainder of the patient's life.

4. Probably the most important consideration for the patient is her mental acceptance of the fact that she will not menstruate or be able to procreate but can have a welladjusted married life. The latter point cannot be emphasized too strongly and these girls should be constantly reassured that they are "normal" females. The mother's anxiety in the case of younger girls may negate the most conscientious efforts of the physician.

Summary

- 1. Two successive siblings with almost identical findings of the testicular feminizing syndrome are presented.
- 2. Laboratory studies failed to reveal any evidence of female nuclear sex chromatin patterns; gonadotropin assays and 17-ketosteroid determinations were essentially normal; the vaginal smears indicated adequate estrogen stimulation.
- 3. This syndrome is transmitted by a recessive sex-linked inheritance with the trait being carried by the X chromosome.
- 4. A general outline as to the management of these patients is given.

I am grateful to Dr. Irving Rothchild for the endocrine determinations, to Dr. Peggy St. Clair for the follow-up studies, and to Dr. Arthur Steinberg for critical analysis of the manuscript.

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Effect of testosterone on experimental endometrial hyperplasia

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The main factor in the etiology of endometrial hyperplasia is an excessive production of estrogen or perhaps an exaggerated sensitivity of the endometrium. Experimental evidence favors the former concept; administration of estrogen has given rise to endometrial hyperplasia in a variety of animals, e.g., the rat, 1, 2 guinea pig, 3, 4 monkey, 6 and rabbit. 5 Its occurrence in women who have been treated with estrogens for a long time adds clinical support to this theory. 7-9

This paper reports the morphologic and some of the histochemical changes produced in the endometrium experimentally and also their modification under testosterone administration.

Material and methods

Twenty-three adult rabbit does, weighing from 2 to 3 kilograms, not spayed, were used. Two of them had littered 2 months prior to the experiment. A control biopsy of the uterus was performed; after this, estrogen was administered in several cycles and each cycle was followed by a biopsy. Each rabbit had from 4 to 6 biopsies.

First cycle. The does were separated from the bucks for 2 months.

Second cycle. Beta-estradiol, 2 mg., was injected every other day for 30 days.

Third cycle. The animals were divided into four groups. In the first three of these groups all animals continued to receive 2 mg. of beta-estradiol every other day; in

addition, the first group was given 2 mg. of testosterone propionate in oil every other day for from 25 to 30 days; the second group was given 20 mg. of testosterone and the third group 40 mg. In a fourth small group all medication was stopped.

Fourth cycle. The beta-estradiol was stopped and the injection of testosterone propionate alone was continued for 26 days in the same dosage as during the third cycle, viz., 2, 20, and 40 mg. every other day. In 4 animals all treatment was interrupted.

Fifth cycle. All treatment was stopped. At the end of a month all animals were sacrificed and complete autopsies were performed.

Throughout the experiment the animals were isolated in cages distant from males. They were fed Purina Rabbit Chow and water freely.

The uterine biopsies were fixed in buffered formalin and stained with (1) hematoxylin and eosin; (2) periodic acid—Schiff (PAS) stain, with and without saliva digestion; and (3) toluidine blue, with and without ribonuclease digestion. Gomori's acid¹o and alkaline phosphatase stains were used in most of the animals.

Results and comment

All the rabbits injected with beta-estradiol developed endometrial hyperplasia, most of them with cyst formation. In all of them the volume and number of endometrial glands were increased. In the control biopsy the average diameter of the uterus measured 5 to 6 mm.; after estrogen this increased to as much as 8 to 10 mm. The increase was

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Fig. 1. Endometrium of rabbit doe before any

due to growth of endometrium and myometrium. In the control biopsy the epithelium was cuboid or flat; after administration of beta-estradiol it was high and pseudostratified, both changes being more marked toward the distal portion of the glands and in the superficial epithelium (Figs. 1-4). Every biopsy specimen also revealed formation of cytoplasmic vacuoles, not stained with hematoxylin and eosin, PAS, or toluidine blue and containing neither acid nor alkaline phosphatase.

In Cycle 3 the rabbits showed no regression of the hyperplasia in spite of the high dosage of testosterone (2, 20, and 40 mg.). In only 3 of them did the hyperplasia continue unchanged; the remaining 16 all showed a slight increase, but 3 rabbits in which treatment was interrupted all showed a frank regression of overgrowth.

In Cycle 4 75 per cent (in which estradiol was suspended and testosterone continued) showed slight regression of the hyperplasia. In 3 rabbits, however, the biopsies showed a slight increase of growth in comparison with the previous biopsies.

All medication was stopped in 4 rabbits of this fourth cycle; they all showed the same reduction of hyperplasia as those that had been given testosterone alone.

Results of these experiments seem to be at variance with common clinical practice which uses testosterone to treat functional bleeding and endometrial hyperplasia. Indeed, we may deduce from them that, in rabbits at any rate, testosterone, even in doses of from 20 to 40 times the estrogen dosage, does not counteract hyperplasia in the presence of estradiol, and that regression occurs only after withdrawal.

Important, but not unexpected, was the observation of an adenocarcinoma in one of the rabbits toward the end of 4 months of experiments. Invasion and metastases had not yet developed at the time the ani-

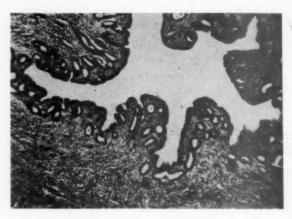


Fig. 2. Endometrium of rabbit after 30 days of estrogen treatment. Hyperplasia and cyst formation are present.

mal was sacrificed. Similar lesions have been reported by Meissner, Somers, and Sherman.¹¹

Periodic acid-Schiff (PAS) secretion. Approximately 80 per cent of the rabbits under beta-estradiol had an intra- and extracellular secretion at the free border of the superficial epithelium and in the cells lying toward the mouth of the endometrial glands. This secretion took the PAS stain and was not digested by saliva. It varied in quantity from traces (1-plus) to larger amounts (4-plus). It was not observed in any of the control biopsies. Under simultaneous action of estrogen and testosterone it increased in some rabbits and decreased in others, but the degree of these changes was not significant. When estrogen was discontinued, the secretion disappeared or diminished markedly. Its presence does not seem to have been commented upon, but it has been reported by McKay and co-workers12 during the proliferative phase and in the endometrial hyperplasia¹³ of women.

Stroma. Important changes also took place in the stroma. In control biopsies it was cellular and compact and contained rather few vessels; after the administration of estrogen it grew thicker and became rather edematous, but the main change was an increase in the number and size of blood

Phosphatases. Acid and alkaline phosphatases responded most actively in this group of rabbits. In the control biopsies acid phosphatase was inactive, while alkaline phosphatase was slightly active (1-plus) in the glandular epithelium and capillaries of the more superficial stroma. Two exceptions were represented by 2 rabbits that had borne a litter 2 months before undergoing the experiment. The endometria of these 2 animals were not hyperplastic, but alkaline phosphatase was highly active (3-plus to

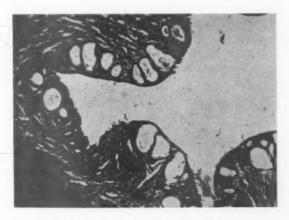


Fig. 3. Endometrium of rabbit. Cystic hyperplasia is marked with abundance of cysts.

4-plus) in the superficial and glandular epithelium and vessels of the stroma. After 30 days of estrogen injection all rabbits developed increased activity of both enzymes up to 4-plus (Figs. 5 and 6). Some differences between them deserve attention; both acid and alkaline phosphatase increased moderately (2-plus) to markedly (3-plus) in the superficial and glandular epithelium and in the surface layers of the endometrial stroma. Acid phosphatase, however, was markedly active in the muscle fibers and arterioles of the myometrium, but not evenly so in all layers of it; the external layer, of circular fibers, showed the maximal reaction, while the internal, longitudinal layer was almost inactive. Alkaline phosphatase, on the other hand, was inactive in the muscular layers and their vessels but intensively active in the capillaries of the stroma.

Activity of the acid phosphatase subsided markedly when all treatment was suspended but, as long as estrogen was given, addition of testosterone produced no noteworthy changes. Activity of the alkaline phosphatase persisted with some individual variation more or less continuously during the whole 4 months of the experiment and even a month longer after estrogen had been withdrawn. Its activity seems to be more prolonged than that of the acid phosphatase.

McKay and associates12, 18 have reported increased alkaline phosphatase activity in the human endometrium during the proliferative phase, in cystic hyperplasia, and in adenomatous hyperplasia.

Ribonucleic acid (RNA). Only slight variations of RNA were observed during these experiments. Moderate amounts of RNA were found in the cytoplasm of the epithelium in the control biopsies; administration of estrogen gave rise to slight increase in most of the rabbits, but this was not significant—at least not with the methods followed. The RNA content fell follow-



Fig. 4. Cystic hyperplasia after estrogen treatment. The epithelium is tall columnar and pseudostratified.

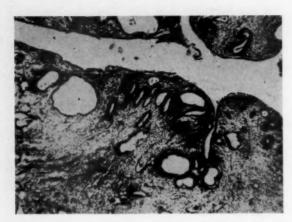
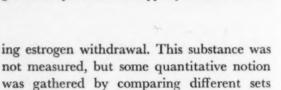


Fig. 5. Hyperplastic and cystic endometrium. Acid phosphatase activity is seen in superficial and glandular epithelium and upper portion of stroma.



of slides.

McKay and co-workers¹² have observed that RNA increases in women during the estrogenic phase and decreases during progestational phase. RNA and estrogen activity seem to be correlated.

Summary and conclusions

- 1. Endometrial hyperplasia produced in unspayed rabbit does by prolonged estrogen administration is not modified by testosterone administration as long as estrogen continues to be given.
- 2. Hyperplasia regresses only after betaestradiol is withdrawn.



Fig. 6. Hyperplastic endometrium. Alkaline phosphatase activity is seen in superficial and glandular epithelium, but mainly in the vessels of the stroma.

- 3. Under the action of beta-estradiol an intra- and extracellular secretion, staining with periodic acid and not digested by saliva, appears in the endometrium; this secretion decreases or disappears on withdrawal of beta-estradiol.
- 4. Beta-estradiol greatly increases activity of both acid and alkaline phosphatase.
- 5. Activity of acid phosphatase is markedly lessened after withdrawal of betaestradiol.
- 6. Ribonucleic acid varies slightly but in more or less direct relation to administration of beta-estradiol.

The beta-estradiol and testosterone propionate were kindly furnished by the Syntex Laboratory of Mexico City.

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Reactivity of puerperal vaginal epithelium to local estrogenic therapy

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RECENT studies in vaginal cytology have raised some doubts about the receptivity of the vagina to estrogens during pregnancy and the puerperium. Some authors claim that during this period the vaginal epithelium is not responsive to estrogens.^{4, 5, 6, 14} Others have even used the "restoration" of vaginal sensitivity to delimit the end of the puerperal condition in the human female.¹⁰

Other investigators have demonstrated that the vaginal epithelium does react moderately after high doses of estrogens during the postpartum period.^{3, 7, 8, 13} Pundel¹² has demonstrated that, in pregnancy, the only missing reactions are karyopyknosis and cornification. He emphasized that, under the hormonal (estrogenic?) environment of pregnancy, the vaginal epithelium develops to heights never attained in other physiologic states. Like others, he believes that the only normal occasion when the vaginal epithelium does not react to administered estrogens with marked proliferation is the immediate postpartum period.

It is well known that, following delivery, the vagina undergoes advanced atrophic changes. Davis and Pearl¹ were the first to demonstrate that this massive desquamation is due to the effect of hormones. Some years before that, Papanicolaou⁰ described the typical vaginal smear changes in the presence

of deep parabasal basophilic cells. In normal conditions, the vaginal smear keeps this subatrophic pattern through the first 15 to 45 postpartum days and even longer if nursing is continued by the mother.

Contradictory results have been reported when cytologic puerperal studies were carried out on patients receiving variable amounts of estrogens to inhibit lactation. Following de Allende's advice,² we attacked the problem by administering the hormone locally. This was done for the purpose of attaining definitive information concerning the potential ability of the puerperal epithelium to react to administered estrogens.

Method of study

To one group of 10 normal postpartum women, we administered daily 5 c.c. of an estrogenic cream by vaginal application (the cream contained 0.1 mg. of dienestrol per cubic centimeter). Prior to each administration, material was obtained for vaginal smear study; this was accomplished with a vaginal glass cannula, aspiration being done from the upper third of the lateral vaginal fornices only. Vaginal fluid was blown onto a clean slide and immediately immersed in alcoholether fixative. The procedure was carried out every day of the patients' hospital stay; when they went home, the vaginal estrogenic therapy was continued. Between the eleventh and the fifteen postpartum day, the patients were scheduled for re-examination and again vaginal smears were collected. The estrogenic therapy was discontinued and the patients instructed to come back after 5 to 7 addi-

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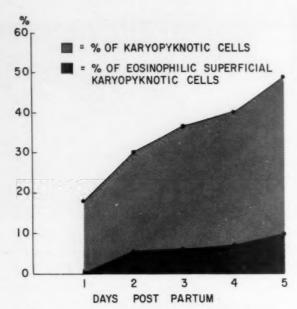


Fig. 1. Ascending curves of karyopyknotic and cornified cells on the first 5 postpartum days. Every point represents the average value measured on 10 patients (800 cells counted for each value).

tional days. At this time, the last smears were collected. The slides were stained according to Shorr's S-2 method and mounted in Canada balsam.

When they were read, careful screening was done in order to ascertain whether or not estrogenic effects were present. No complication arose from the vaginal medication since at the time of taking each new smear the cream already had been eliminated together with the puerperal secretions, or had been absorbed. Every patient during the period of this study was nursing her baby and no reduction of the milk output was found. The lochia was noted to become scant and odorless.

The amount of aspirated blood which contaminated the cytologic contents of the vaginal fluid made the exact evaluation of the hormonal effects more difficult. This was overcome by increasing the number of vaginal cells counted, in order to get more uniform and reliable results. A total of 1,600 cells were counted on each smear, 800 for the cornification index and 800 for the kary-opyknotic index. We used the improper but accepted term "cornified," to describe the eosinophilic superficial cell with a kary-

opyknotic nucleus. We classified as karyopyknotic every cell whose nucleus was smaller than 6μ and/or showed an opaque structureless chromatin pattern. Attention was also paid to the general aspects of the smears, the presence of inflammatory cells, and the occurrence of lactation-type cells.

Results

A definite estrogenic effect could be seen in the vaginal smear from the very first postpartum day. A completely proliferative pattern was established between the third and the fourth postpartum day. After that, the polygonal intermediate and the superficial basophilic squamous cells completely dominated the field. Some lactation-type cells were found until the third and fourth postpartum days, but a typical lactation-smear was never obtained. Some deep basal and parabasal cells were seen but their number steadily decreased until the fourth postpartum day, when they could no longer be seen. Comparing the smears obtained with normal postpartum ones, we could recognize a marked decrease in the number of inflammatory cells; these were practically absent

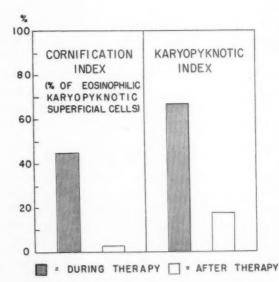


Fig. 2. Comparison of the estrogenic effect on patients receiving estrogens (shaded columns) with the condition attained by the same group of patients 5 days after discontinuance of therapy (empty columns). The shaded columns represent the average reached at the end of local estrogenic therapy (eleventh to fifteenth postpartum day).

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on ith papy ent nic from the fourth postpartum day on. As mentioned above, we were surprised to see how few chorionic, decidual and endocervical cells were present.

Fig. 1 represents the curves obtained for cornification and karyopyknosis (averages of 10 patients). The daily individual variations were not sufficient to modify the general shape of the curve, which showed a steadily ascending pattern in the first postpartum days.

The smears taken between the eleventh and the fifteenth postpartum days, while the patients were using the estrogenic medication, exhibited a strong proliferative reaction, with high indices of karyopyknosis and cornification. The general pattern of the smear resembled that found near ovulation (preovulatory smear). After discontinuation of therapy, a marked vaginal involution followed and every patient had a subatrophic type of smear, with the presence of so-called lactation-type cells. The indices of cornification and karyopyknosis during and after estrogen therapy are compared in Fig. 2.

The rapid fall of the above-mentioned indices leads us to the assumption that the observed effect was produced by the administered estrogen and not by endogenously produced hormones.

From the analysis of our results, it seems

evident that the vaginal receptivity to estrogens is not impaired during the postpartum period. The reason why oral or parenteral estrogens do not elicit similar proliferative reactions must be found in some other mechanism than vaginal irresponsiveness, since we believe we have demonstrated that the postpartum vaginal epithelium reacts normally to local estrogenic therapy, just as in any other period of the life span of the human female.

Summary

To study vaginal receptivity to estrogens, we have made an evaluation of local estrogenic therapy on 10 postpartum patients. To each, 0.5 mg. of dienestrol in cream was administered daily, by vaginal application. The estrogenic effect was evaluated by vaginal smears. The analysis of results has clearly shown that the vaginal epithelium at that period is normally responsive to estrogens and that the failure of oral or parenteral estrogens to produce similar proliferative reactions is due to some factor other than nonresponsiveness of the vaginal mucosa.

We are indebted to Johnson & Johnson do Brasil S/A for providing the cream for vaginal administration, and to Prof. M. E. Krahl and Miss Ardis Lostroh, Ph.D., for their help in the translation of the original manuscript.

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Control of immediate postoperative pelvic pain by local anesthetic infusion

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IFPELVIC pain can be alleviated during the first 48 hours after a vaginal hysterectomy, the postoperative physical discomfort following this well-standardized procedure is almost eliminated. However, the narcotics routinely used for this leave much to be desired.

Since local anesthesia is usually effective, prompt, and safe for the relief of pain, it was thought that postoperative discomfort might be controlled if a local anesthetic agent could be infused in and about the incised vaginal cuff and the ligamentous stumps sutured to the cuff. Moreover, since most of the incisional surfaces point near the margin of the vaginal incision, infusion through a Ttube appeared worthy of a trial. This was done on 100 consecutive patients who had vaginal hysterectomies with and without vaginoplastic repair and with and without adnexal resections and compared with 100 similar patients in whom lidocaine* was used for the relief of pain.

Review of the literature

The anesthetic agent of choice, lidocaine, was synthetized by Lofgren in 1943. It is the most stable local anesthetic agent known and may be stored almost indefinitely. It has a short latency period and rapid diffusion

qualities; it is of low toxicity,2 and it produces profound anesthesia.

While a review of the literature reveals no similar application of lidocaine in controlling postoperative pain, Hanson and Hingson³ have applied it as a topical anesthesia in 7 instances in the peritoneal cavity with good results. They used it in 2 poor-risk patients in whom minimal anesthesia was indicated because they were in shock. Surgical manipulation, however, set up such intolerably painful stimuli that 60 c.c. of 2 per cent lidocaine solution in one case and 50 c.c. of 2 per cent lidocaine solution in the other was



Fig. 1. Pelvic peritoneum and ligamentous stumps exposed.

From the Department of Gynecology of St. Elizabeth Hospital.

This project was supported by a grant from Astra Pharmaceutical Products, Inc.

*Supplied by Astra Pharmaceutical Products, Inc., as Xylocaine.

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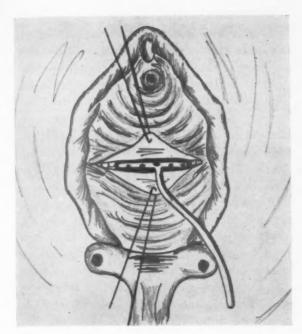
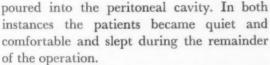


Fig. 2. Insertion of the T-tube.



However, one patient in the Hanson and Hingson³ series had become nauseated and developed some vertigo, drowsiness, hyperactive reflexes, and a crying jag that lasted minutes. The symptoms were transient but prompted these authors to warn of the possible toxic manifestations in the occasional case.

Material and methods

This study includes 200 private patients (J. J. McD.). The surgical technique, therefore, is the same throughout the entire series. The average age of patients in the study group was 43.1 years and for the control group 43.6 years (Table I).

A small No. 14 French T-tube is used for infusion of the anesthetic solution into the pelvis. It is placed in the cul-de-sac after half of the interrupted sutures are placed in the transverse vaginal incision. Multiple perforations are made in the 4 cm. cross segment of the T-tube to allow for a wider area of infusion. The tube, 12 cm. in length, is



Fig. 3. Closure with T-tube in place.

brought out through the vagina and connected to an infusion drip apparatus (Figs. 1-3).

The two interrupted sutures immediately adjacent to the T-tube are closed over a hemostat. This allows relative freedom of movement of the tube and permits easy removal in 48 hours. At this time, gentle, firm traction is applied to the T-tube and the patient is asked to take a deep breath. In all but one of the 100 patients under study, the tube was removed without pain or difficulty. In this patient one suture in the vaginal cuff had to be cut to remove the tube.

The local anesthetic solution consists of 50 c.c. of 2 per cent lidocaine hydrochloride diluted in 250 c.c. of normal saline. It is allowed to run at 20 to 22 drops per minute every other hour for the first 48 hours. Aspiration of the T-tube is done every 4 to 8 hours, depending upon the amount of fluid obtained from the cul-de-sac. The patient obtains not more than 1,000 mg. in a 24 hour period. Patients are allowed supplementary medication for pain if they ask for it and are not discouraged from doing so. The nursing supervisors on the floors were asked to observe the patients closely and to

Table I. Type of surgical procedure with and without the use of lidocaine pelvic peritoneal infusion

	Number of cases		
Operations	Study	Control	
Vaginal hysterectomy	59	62	
Excision of cervical stump	3	1	
Vaginal hysterectomy with repair	22	28	
Vaginal hysterectomy with salpingo-oophorectomy	16	9	
Total	100	100	

Table II. Postoperative results with and without use of pelvic peritoneal lidocaine infusion

	Milligrams of narcotics in 48 hours		
Operations	Study	Control	
Vaginal hysterectomy (including excision of cervical stump)	207.5	552.7	
Vaginal hysterectomy with repair	190.9	601.7	
Vaginal hysterectomy with			
salpingo-oophorectomy	183.3	552.8	
As a whole	201.0	567.3	

allow none of them to go without narcotics to alleviate their discomfort.

Results

In order to evaluate the relief obtained with this procedure, we compared the amounts of narcotic medication given for pain to patients who received the anesthetic infusion with that given patients in the control series who received only narcotic medication (Table II).

Complications and morbidity

There were no complications encountered with the use of the T-tube or the anesthetic infusion.

The morbidity in the series was 20 per cent. That was a slight increase as compared with the study by McDonough, Chiasson and Beach.⁴ Previous studies without the use of the T-tube showed a morbidity of 18.2 per cent.

Comment

This study was made in an effort to diminish the immediate postoperative discomfort of patients following vaginopelvic operations. However, there was a wide divergence of results in individual patients, due in part to the variable pain tolerances of the patients and in part to technical difficulties. However, all of the patients showed marked relief with a local anesthetic infusion into the cul-de-sac.

Early in the study it was noted that during the hour in which no solution was allowed to run into the cul-de-sac the patient often would turn the infusion on herself to obtain relief. This was discouraged promptly and the nurses were instructed to watch for this irregularity and to remove the infusion apparatus from the room if necessary. In two instances the patients allowed the entire 250 c.c. infusion to run in within the course of 8 hours. No ill effects were noted, and the patients were completely free from pain.

Postoperative bleeding was detected by means of the T-tube in two instances and appropriate measures were taken to control the bleeding. The T-tube allows measurement and replacement of the blood loss and appears to prevent the establishment of large clots which, in wicklike fashion, often promote continuous bleeding. It is now felt by the resident staff that the T-tube should be used after all vaginal hysterectomies. It does not complicate the patient's recovery and can be easily removed after 48 hours.

Conclusions

- 1. Infusion of the cul-de-sac with a local anesthetic solution in the immediate post-operative period following vaginal hysterectomy affords the patient relief of pain and reduces substantially the amount of narcotics normally required.
- 2. The infusion is delivered to the culde-sac by means of a No. 14 French T-tube left in situ when the vaginal incision is closed.
- 3. Lidocaine hydrochloride (50 c.c. of a 2 per cent solution) in 250 c.c. of normal saline is used as a continuous drip every

other hour during the first 48 hours. This procedure reduced the amount of postoperative narcotics to about one third of that in the control series.

4. No reactions to the lidocaine or to the

use of the T-tube occurred in a series of 100 patients.

5. Regular use of the T-tube has been distinctly helpful in discovering early post-operative hemorrhage.

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New instrument for incising the vaginal cuff during total abdominal hysterectomy

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The usual technique for removing the cervix during a total abdominal hysterectomy for benign disease employs the use of scissors following a stab opening into the anterior vaginal fornix. This method is often awkward, particularly in a deep pelvis, and also has the disadvantage that sometimes too much vaginal tissue is removed and an irregular or ragged cuff is left behind. Some surgeons therefore prefer to use a scapel instead of scissors, but this method is not without risk because of the tendency of surgeons to excise more vaginal tissue than desired.

A knife was therefore devised which does away with the disadvantages of both scissors and scalpel and enables the surgeon to remove the cervix accurately and safely. In principle, it resembles a grapefruit knife (Fig. 1). It has a fairly heavy, curette-like handle and a somewhat rigid shaft to which the blade is joined. The blade is made of stainless steel so that the edges will remain sharp. Both ends are blunt for about one half inch, in order to avoid damaging adjacent tissues.

A small incision is made into the anterior wall of the vagina with an ordinary scalpel. Through this opening the new knife is introduced and since the blade is curved on the flat it can be kept closely applied to the cervix. The handle of the knife is held parallel to the cervix while its sharp edge cuts the vaginal attachment to the cervix with a sawing motion. The cutting edges are bev-

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Fig. 1. A, Front view. B, Rear view.

elled on both sides so that the instrument can easily be used in either direction without removal from the vaginal opening.

This instrument is not recommended if hysterectomy is being performed for malignant disease as its object is to conserve the entire length of the vagina.

This knife is manufactured by J. Sklar & Company, Long Island City, New York.

Wedge resection of the uterine fundus in the therapy of intractable menorrhagia

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Washington, D. C.

MENORRHAGIA of the chronic, progressive type in the absence of significant pelvic pathologic conditions has long been a source of concern both to the physician and to the patient. It has usually defied accurate classification, and through expediency or incomplete understanding has generally been included with all types of uterine bleeding of unexplained etiology under the nebulous if not actually misleading name of dysfunctional bleeding.¹

The agent or agents underlying the clinical picture have been sought in the endocrine system and the consensus at this time weighs heavily in this direction.²⁻⁴ Increased fibrous tissue proliferation,^{5, 6} subinvolution following childbirth,^{6, 7} and hypertrophy of the myometrium⁸ have all become incriminated at one time or other for a share in the blame. Changes in the vascular walls have also been pointed out.^{9, 10}

With so much confusion regarding the etiology of the condition it is little wonder that specific steps toward its amelioration have not evolved. Curettage of the uterus, usually repeated, forms the basis of all means of diagnosis and therapy. It should hardly be necessary to point out that although such a procedure may produce remissions, there is no evidence to show that it is more than a stop-gap procedure.^{1, 11, 12} Hormone therapy, from estrogens through progesterone to an-

drogens, has been used with little more than mediocre results.^{1, 12} Caustic solutions have been instilled into the uterine cavity with some efficacy but have been found to carry undue risk in all but the most expert hands.^{1, 12} Hysterectomy is an effective method for control of the bleeding, but it is frequently distasteful and is frowned upon by patient and physician alike in the absence of an understandable anatomic lesion.

For the past 6 years an operative procedure has been carried out which has been designed to reduce the bleeding surface of the uterine fundus without interfering with the natural function of the organ. Fundectomy for excessive bleeding has been utilized for many years. However, it has never been widely used and, in recent years, rarely if at all. Wedge resection of the uterine fundus in congenital anomalies of the uterus for recurrent abortion and for bleeding was advocated in 1907, and has been used sporadically since that time. 13

In carefully selected patients wedge resection of the uterine fundus has been shown to be of value. The criteria for selection of patients as well as the operative technique and the results are reported in this communication.

Materials and methods

Seven patients varying in age from 28 to 32 years have undergone wedge resection of the uterine fundus and have been followed from 6 months to 6 years.

The criteria for selection of these patients

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have been that (1) over a period of more than a year they have found it necessary to severely restrict their activities for 2 or more days because of excessive bleeding in spite of rational drug therapy; (2) they use 36 vaginal pads or more for each menstrual period; (3) they have a uterus of 10 cm. in diameter by clinical examination; (4) they have no gross endocrine abnormality as determined by basal temperature graph, curettage specimen, and vaginal smear; and (5) no other significant pelvic or systemic conditions which might account for the excessive bleeding are present.

Although we have made exception to this rule, we further believe that the procedure should be carried out only when the patient is under 35 years of age and is desirous of having other pregnancies.

Following a routine preoperative work-up which includes blood coagulation studies, thyroid and ovarian evaluation, and review of previous curettage specimens, the patient is examined one month with the menstrual flow at its height without medication and the following month at the same period while taking Ergotrate. This procedure serves to

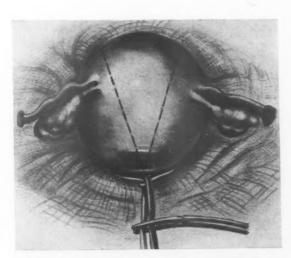


Fig. 1. A "V" is marked off on the posterior surface of the uterus, starting at the peritoneal reflection (marking the internal os), being carried to the fundus just inside the insertion of the tube and uteroovarian ligament, and continuing over the posterior aspect of the organ to end in a similar "V" in the midline at the anterior peritoneal reflection.

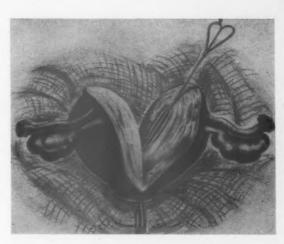


Fig. 2. The insertion of a probe in the groove which runs from the tubal junction with the endometrium to the cervical os makes it possible to excise all endometrium but that hidden by the width of the instrument. In this fashion the amount of surface left to bleed is reasonably constant from one instance to the next.

rule out any question of the severity of blood loss during menstruation and corroborates or casts doubt on the patient's own evaluation.

Operative procedure

The peritoneal cavity may be opened by means of any recognized lower abdominal approach although it is well to incise the fascial layers at such a point that the sacral promontory may be exposed without too much difficulty if a presacral neurectomy is to be carried out.

The broad ligaments are perforated bilaterally at the level of the peritoneal reflection on the anterior surface of the uterus, and a French catheter (No. 16) is applied as a tourniquet before any procedure is carried out on the uterus itself.

The "V" (Fig. 1) is then marked out from the region just above the internal os both on the anterior and the posterior aspect of the uterus to a point on the fundus just inside the insertions of the round ligament and the tube. The uterine cavity is first entered at the tip of the "V" and a probe inserted so that its tip may be felt to mark the cornu. In this fashion the fundal incision may be made just medial to the valve at the

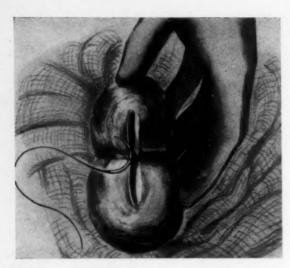


Fig. 3. Approximation of the opposing walls is begun at the cervical junction. An attempt is made to stay just inside the submucosal con-nective tissue which is evident visually as a fine light line, and the sutures are taken on a slight angle to this line (rather than parallel to it) to reduce avulsion of the friable tissue. After the first knot is made and a second suture is taken, the procedure is begun on the opposing side of the endometrial cavity. In this fashion, undue stress is avoided on the already placed sutures by the mechanical procedure of accommodating the evertightening "V" to the curve of even a small needle. The two lines of sutures reach the superior aspect of the cavity simultaneously and may be tied together and thereby reduce the number of buried knots. A second layer of sutures (not shown) is then started in the same fashion lateral to the first line of approximation. These, taken as hemostatic agents and to approximate the muscle and bury dead space, are angled more and are allowed to penetrate the body of the uterus more deeply than the delicate submucosal stitch. Here too, the two sutures are started simultaneously on each side of the cavity and reach the dome of the fundus to be tied together.

tubouterine junction. With the probe lying on the lateral margin of the ipsilateral uterine wall the knife may be allowed to remain medial to the probe and thereby excise all the myometrium and endometrium mesial to it. When this maneuver is repeated on the opposite side it is possible to excise all the endometrial tissue except that contained in the lateral grooves of the uterus that extend from the tubal junction to the internal cervical os (Fig. 2).

With use of Atraumatic suture of 5-0 chromic gut to approach the submucosal

layer (appearing as a fine white line just under the gray of the endometrium) on a slight angle, the cavity is approximated from the apex of the "V" to the fundus. The technique of suturing has been found to be simplified if both the right and left sides of the incision are sutured concomitantly; it is difficult to insert even a small curve between the cut surfaces of the myometrium without placing strain on the previously laid down suture line if one side gets too far in advance of its counterpart (Fig. 3).

A second layer of 5-0 chronic suture is then placed (again in an angular fashion) to act as a hemostatic suture and to approximate the major mass of the myometrium. Here again it is profitable to begin each right and left suture concomitantly at the apex of the "V" and to carry them to the dome of the fundus. The third line of sutures is used to approximate the serosal surfaces, and here an inverting mattress suture of the same fine chromic gut is used (Fig. 4). The tourniquet is released and the perforations in the broad ligaments are closed.

A presacral neurectomy and section of the uterosacral ligaments are performed. A standard closure of the incision in layers is then carried out. No particular postoperative precautions are taken.

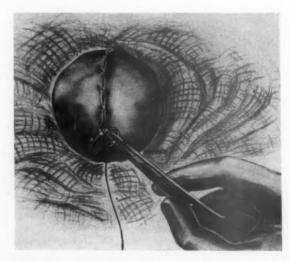


Fig. 4. An inverting mattress suture is used to approximate the serosal edges and act as a hemostatic agent for the more superficial portions of the myometrium.

Table I. Clinical data in instances of idiopathic myometrial hypertrophy and control groups of adenomyosis and anatomically normal uteri

	No. of cases	Age (years)	Parity	Menstrual abnormalities			
				Menorrhagia (%)	Metrorrhagia (%)	Pain (%)	Clots
Normal	10	39	2.7	0.0	30.0	30.0	10.0
Idiopathic myometrial hypertrophy	47	38	3.2	47.0	31.0	49.0	53.0
Adenomyosis	10	38	1.8	10.0	20.0	40.0	40.0
Operated series	7	29	2.1	100.0	0.0	70.0	100.0

Table II. Tissue characteristics of idiopathic myometrial hypertrophy, normal controls, and adenomyosis

	Weight of uterus (grams)	Endometrial abnormality (%)	Connective tissue (%)*	Vascular changes (%)	Fiber	Nuclear diameter	Nuclear concentra- tion
Normal Idiopathic myometrial	66	10	20	70	3.4	5.0	2.8
hypertrophy	170	20	80	40	3.5	4.3	2.9
Adenomyosis	103	20	70	40	3.4	4.9	2.3

*The percentage of connective given here is not in relation to myometrium but the incidence of uteri in which the amount of fibrous tissue proliferation was in excess of an average obtained from the "usual normal" in the control series.

Results

Four of the 7 patients on whom the wedge resection of the fundus has been carried out noted a reduction of menstrual flow at the time of the first postoperative menstruation to less than 18 vaginal pads for the cycle. The remaining 3 used between 24 and 36 vaginal pads for this first period.

After the first postoperative menstruation there was a reduction to less than 18 vaginal pads per cycle in all patients but one. There was a continued gradual reduction for a period of 6 months to the point where only one patient was using more than 12 pads a month.

Blood loss failed to be reduced for this one patient, and at the end of one year she was bleeding at approximately the same rate as prior to the procedure.

Five of the 7 patients had noted moderate to severe dysmenorrhea prior to operation. Following the procedure no patient complained of more than minimal distress concomitant with menstrual bleeding.

In each instance the postoperative uterine corpus was reduced to approximately normal size (5 by 5 cm.).

Two of the patients became pregnant following the procedure, one 2 years postoperatively, the other at 4 years. Both followed a normal antepartal course and were delivered by cesarean section. Following the puerperium neither uterus returned to the prepregnancy dimensions, but still failed to return to the marked preoperative enlargement. There has been no recurrence of the menorrhagia up to the present time.

Comment

Since 1860, when the symmetrically enlarged uterus was first recognized, there has been scant agreement as to the cause of its anatomic alteration. Commonly, the diagnosis of "fibrosis uteri" is seen on clinical records and that of idiopathic myometrial hypertrophy on reports from the department of pathology. Many qualified men, both clinicians and pathologists, refuse to recognize the entity under any name.

Although approximately one half of all patients who have dysfunctional bleeding are found to have significant uterine enlargement, only about one third of patients with uterine hypertrophy complain of ex-

cessive bleeding.3 It is not unknown for menorrhagia to occur in women with normal or even excessively small uteri. In order to roughly test the thesis that alterations in the anatomy of the parous uterus have little or no part in the functional activity of the organ, a group of uteri that had been removed for various reasons but which had received the pathologic diagnosis of idiopathic myometrial hypertrophy were studied. As control material, a group containing endometriosis interna were subjected to the same scrutiny. A second series was selected of normal-sized uteri removed with the clinical and pathologic diagnosis of carcinoma in situ of the uterine cervix with no specific symptoms. Duplicate sections were cut on each specimen at 5 μ ; one was stained with hematoxylin and eosin, the other with Masson's trichrome stain.

Two examiners independently studied the material by number, being unaware of the source of the individual block. Myometrial diameters and nuclear width were determined by an ocular micrometer, and the ratio of vessel wall to lumen was estimated by the same mechanism. The proportion of connective tissue to muscle was estimated for the submucosal region, the myometrial layer, and the subserosal aspect. The pattern of the endometrium was classified as proliferative, secretory, mixed, or atypical.

Table I crystallizes the pertinent clinical data on the patients of the three groups, and Table II summarizes the histologic characteristics of the tissue studied by these techniques. It is evident from the clinical data that patients with idiopathic myometrial hypertrophy have a higher incidence of menorrhagia than either the normal patients or those with adenomyosis, although dysmenorrhea, metrorrhagia, and clotting are not significantly different. Analysis of the histologic data fails to show a significant difference in width of muscle fiber although increased proportion of connective tissue is present in both series in which uterine enlargement occurs. It is significant to note, however, that even the changes in the connective tissue are not great enough, either collectively or in the individual instance, to account for the increment in weight and size of the uterine body; hyperplasia of both the muscular elements and the fibrous tissue would be necessary to account for the change.

Schwarz⁷ in an extensive study of the symmetrically enlarged uterus arrived at this conclusion, but his work seems to have been lost in the more recent literature on the subject. He regarded the major etiological agent as a failure of complete involution following pregnancy although an occasional instance of primary myometrial hypertrophy and chronic metritis (characterized by round cell infiltration in the myometrium) was encountered.

We feel that this interpretation fits both the clinical data and the histologic alterations noted in our series better than either the thesis of hormonal imbalance or the concept of pelvic congestion. On this basis it is felt that mechanical reduction of the bleeding surface of the uterus becomes physiologic rather than empiric.

Unfortunately, we are unable to explain the single failure. The histologic data in this case deviated in no way from data in cases in which a symptomatic cure was obtained by the procedure, and re-evaluation of the endocrine values postoperatively has failed to show even a temporary deviation of significant magnitude to account for the profuse flow. It is believed that this instance makes it desirable to assume that the procedure will not assure cure to all patients even when they are carefully selected and properly screened.

Conclusions

Mechanical reduction of endometrial tissue of the symmetrically enlarged uterus will usually correct the menorrhagia which may occur in those individuals who complain of a serious degree of cyclic blood loss.

A procedure is described to carry out this effect which conserves not only the menstrual cycle but also the ability to carry further pregnancies.

The use of the terms, "fibrosis uteri," "idiopathic myometrial hypertrophy," and

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"chronic metritis," which have caused the academic repudiation of the existence of symmetrical enlargement of the uterus, with or without symptoms, should be discontinued.

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Acute nonpuerperal inversion of the uterus

A case report

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The following report is that of an unusual and interesting case of acute inversion of the nonpuerperal uterus, due to a large submucous myoma, for which a vaginal hysterectomy was done as an emergency procedure to control hemorrhage. Reports of this condition are few, particularly in the English literature. Levin,³ in 1955, collected 61 cases from the world literature and reported a case of his own. Since the above report I have been able to find only 5 additional cases in the English literature. The second case of the postpartum type, which is less rare.

V. P., a 32-year-old Negro woman, was admitted to Charity Hospital at New Orleans on March 29, 1958, having been transferred from an outlying Charity Hospital with profuse vaginal bleeding and a diagnosis of "Grade IV fungating lesion of the cervix." She had been given 2,000 ml. whole blood; the vagina was packed, and she was referred to the New Orleans Charity Hospital when it appeared that blood loss exceeded replacement.

Past history revealed hypermenorrhea and polymenorrhea of 5 months' duration. Four days prior to admission, she had experienced lower abdominal cramps and vaginal bleeding of increasing severity.

On admission, physical examination revealed an obese patient with blood pressure 140/110, pulse 140 per minute, and hematocrit 28 per cent. Pelvic examination revealed a large, firm cauliflower mass approximately 8 by 8 cm. presenting in the vagina at the level of the iliac spines. A thin dilated cervix could be palpated above this mass. The impression at this time was that of a submucous leiomyoma presenting through the cervix. Because of active, uncontrolled bleeding the patient was prepared for operation immediately with the intention of amputating the fibroid vaginally to control hemorrhage. By the time she had arrived in the operating room, the mass had been completely delivered and was protruding 6 cm. out of the introitus (Fig. 1). Upon examination, with the patient now under anesthesia, it was apparent that there was a complete inversion of the uterus (Fig. 2). Bleeding had stopped spontaneously, apparently because of incarceration of the tumor and uterus. A ligature was placed above the tumor, and the latter was amputated. The fundus was amputated with the

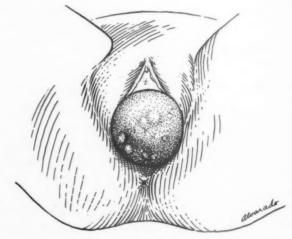


Fig. 1. Drawing of tumor as it presented through the introitus as the patient was prepared for operation.

From the Department of Obstetrics and Gynecology, Tulane University, and Charity Hospital of Louisiana at New Orleans. m n. he be

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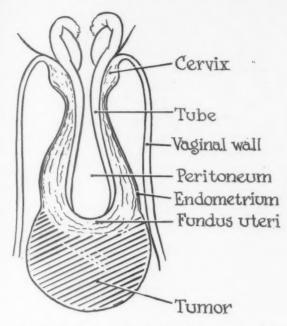


Fig. 2. Diagrammatic sketch showing complete inversion at the time of operation.

remainder of the uterus still inverted. The uteroovarian and round ligaments were then cut and sutured through this opening in the fundus and a vaginal hysterectomy done without correction of the inversion. The bladder was dissected from above, as in the usual abdominal approach. Difficulty was encountered in identifying the cervicovaginal junction because the cervix was almost completely effaced. The peritoneum was closed with a purse-string suture, the round and cardinal ligaments approximated, and the vaginal cuff left partially open. Total blood replacement was 3,000 ml.

The patient progressed very well postoperatively except for deep thrombophlebitis of the right leg which responded to paravertebral blocks, and she was discharged on the seventh postoperative day. Follow-up examination in the clinic was negative except for granulation tissue at the vaginal cuff.

Summary

A case of inversion of the uterus in the nonpuerperal state due to a large submucous fibroid is presented. This is an unusual complication of uterine myomas as evidenced by the fact that there are now only 68 cases reported in the English literature, most of them chronic. Hemorrhage was profuse in this case, necessitating an

immediate vaginal hysterectomy, done without correcting the inversion, with an excellent result.

Addendum. The patient returned to Charity Hospital Sept. 26, 1959, having developed a large

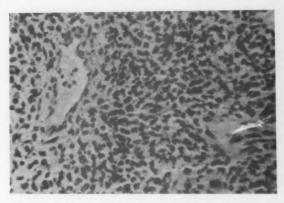


Fig. 3. Pelvic mass showing undifferentiated sarcoma. (×340; reduced ½,.)



Fig. 4. The original tumor, a rhabdomyosarcoma, with undifferentiated sarcoma cells on the left and differentiated ribbon-shaped cells on the right. (×340; reduced ½5.)



Fig. 5. Higher magnification showing striations in tumor cells. (×930; reduced ½5.)

abdominal mass. Exploration revealed generalized abdominal carcinomatosis. Biopsy disclosed undifferentiated sarcoma (Fig. 3). Since the origin was unknown the original slides were reviewed by Dr. William H. Sternberg, Tulane University Department of Pathology, and were

found to contain a previously overlooked sarcoma containing striped muscle elements (Figs. 4 and 5). The patient's course was rapidly downhill and she died on Oct. 24, 1959.

This represents a case of rhabdomyosarcoma of the uterus with acute inversion.

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Pelvic perfusion with nitrogen mustard for cancer: a neurological complication

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There are few reports of complications attending the use of nitrogen mustard (HN₂) by the perfusion technique except for occasional generalized bone marrow depressions where circulatory isolation was incomplete. To solve the solve that the solve that they do possess a strong neurotoxicity. It is possible that this, rather than bone marrow damage, may become the limiting factor in the dosage of HN₂ in perfusion procedures.

This report concerns a patient who sustained peripheral nerve damage while undergoing pelvic perfusion with HN₂ for a metastatic endometrial carcinoma.

Case report

History. A 47-year-old white woman was admitted to the hospital Oct. 9, 1958, with acute abdominal pain. A large pelvic mass was found. A right ovarian tumor, measuring 18 cm. in diameter, had undergone acute torsion as determined by laparotomy. There were implants of tumor on the left ovary and pelvic peritoneum. The uterus and adnexa were removed. Histologic study showed an adenocarcinoma of the endometrium with massive intracapsular right ovarian metastasis.

Department of Obstetrics and Gynecology, Memorial Research Center and Hospital, The University of Tennessee.

Presented at a meeting of the Obstetric and Gynecologic Section of the Tennessee State Medical Association, April 14, 1959. Three weeks postoperatively the patient was subjected to pelvic perfusion, because of known intraperitoneal spread. Sixty milligrams of HN₂ in isotonic saline was administered in 4 equally divided doses at 15 minute intervals. The drug was introduced into the arterial side of the extracorporeal circuit.

Method of perfusion. The pelvic circulation was isolated by occlusion of the aorta and vena cava above their bifurcations with Potts clamps. The lower extremities were excluded from the circuit by pneumatic tourniquets applied to the upper portion of the thighs. Bardic plastic catheters were introduced into the right femoral artery and vein, after being rinsed with heparin, and connected to the pump circuit. Fresh heparinized blood was used to prime the pump and lung. A flow rate of approximately 500 c.c. per minute was maintained. This is adequate for normal oxygenation, carbon dioxide removal, and maintenance of pH.4, 5, 14 Following introduction of the final dose of HN2, the perfusion was continued for another 15 minutes. This was done to allow for decay of any residual alkylating agent. Hemolysis was negligible during the procedure. There was no drop in platelet or white blood cell count during the perfusion.

Course after perfusion. Maximum hemopoietic depression occurred about the eleventh day following operation. The platelets fell to 48,000 per cubic millimeter and the white blood count to 1,200 per cubic millimeter. The blood count returned to normal value by the seventeenth day. Examinations of the bone marrow indicated that depression was confined almost entirely to the pelvic area and was most acute on the seventh day. There was moderate recovery at 17 days.

The patient developed pustules of the skin over the sacrum, perineum, and upper thigh

NEUROLOGIC EXAMINATION: Right Leg Left Lea MOTOR: Radiomimetic effect Gluteus maximus Peroneal F.D.B. Gastrocnemius - 2 17.50 cm 18.25 cm - 2 Hamstrings -2 11.50 cm -12.00 cm D. T. R. _ Absent Babinski_ Negative SENSORY: Hypoesthesia _ lateral Hyperesthesia to pin prick aspect of right leg. Below on top and bottom of foot knee_ loss of touch in on left leg.

Fig. 1. A diagram showing the area of neurological changes produced by the nitrogen mustard. They are limited to the area isolated for perfusion.

subsequent to the perfusion. These were believed to be secondary to necrosis caused by the high HN₂ dosage. These lesions persisted for approximately a month. The patient left the hospital ambulatory on the eighteenth day. A follow-up visit was scheduled for 2 weeks later. This was disregarded by the patient.

Vibration sense_normal

On Jan. 3, 1959, 2 months after discharge from the hospital, the patient returned because of pain and inability to use the right foot. The disability had become progressively worse in the previous month. In retrospect, it was recalled that she had complained of severe pain in the right leg after the operation. At that time there was no clinical evidence of thrombophlebitis and no neurological deficits. On the contrary, it was the opinion that the pain was due to a mild peripheral neuritis from ischemia during operation.

Examination on the last admission revealed sensory changes and atrophy of the muscles and complete foot drop of the right lower extremity. There was diffuse, spotty weakness of the muscles of the left leg and thigh. The radiomimetic effect of the drug, as manifested by a discrete area of tanning over the pelvis, suggested that satisfactory regional isolation had been attained. Nerve damage was therefore expected to be intrapelvic.

It was concluded that the damage had occurred to the lumbosacral plexus. The right-sided transient sensory disturbances finally cleared.

The right gluteals and quadriceps remained weak while the hamstrings and muscles below the knee were paralyzed. The left quadriceps were weak. No disturbances of perineal sensation or function of the anal sphincter were detected (Fig. 1).

A consultant in physical medicine found a reaction of degeneration of the motor nerves. This was most severe in the sacral portion of the lumbosacral plexus. Gluteal involvement was thought to exclude paralysis attributable to the application of the tourniquet.

Extensive physical therapy with muscle reeducation was given to the right leg and before discharge a long leg brace was fitted. At a recent follow-up visit, the patient was able to walk with the aid of crutches. According to the neurological consultant, recovery will at least be partial. There was no evidence of recurrence of the malignancy at this time.

Comment

Purposely, a cancerocidal dose of HN₂ was delivered to the tumor short of producing

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lethal, generalized, bone marrow damage. Almost total depression of the pelvic bone marrow is considered tentatively a good criterion for measuring the efficacy of therapy. Holland and Regelson¹⁰ found the greatest tumor effect when the hemopoietic depression was most pronounced. The bone marrow is thought to mirror the efficacy of the drug. Others have demonstrated that simple intraarterial injection of mustards into the circulation of certain tumors causes, at best, only temporary tumor regression.2, 7, 12, 13 Intravenous HN₂ has been palliative in a limited number of tumors. Dosage is limited by the cytotoxic effect of these drugs on the whole body.3 The use of an auxiliary circulation for the tumor area through which the alkylating agents may be administered permits higher local dosage with less general effect on the body. This is analogous to shielding in x-ray therapy. The use of a heart-lung machine makes possible maximum tissue oxygenation and elimination of carbon dioxide in the isolated body region. This is important, because it has been shown that

high oxygen saturation is necessary for maximum radiation effect.^{1, 4, 9, 10} The radio-

mimetic drugs would be expected to exert

the greatest activity with full oxygenation.

Woodhall¹⁸ demonstrated in acute experiments the neurotoxicity of alkylating agents by perfusing the brains of dogs with HN₂. Animals treated with high dosage of HN₂ developed seizures and electroencephalographic changes, and failed to survive. He felt that HN2 in high dosage was capable of causing damage to peripheral nerve tissue as well as to the central nervous system. Klopp, 11 also, produced changes in the brains of dogs by perfusing them intra-arterially. He found that the animals treated chronically with HN₂ by intracarotid injection developed atrophy of the cerebral and cerebellar hemispheres and basal ganglia on the treated side. He did not find any extracranial nervous system lesions by autopsy examination. For these reasons he instituted the use of regional perfusion. As the use of isolation procedures become more prevalent and a wider variety of drugs are studied, it is expected that more new side effects will be encountered.

Injury of tissue is explained on this basis: Alkylating agents have an affinity for nucleic acid and nucleoproteins of cells. Experiments, in vitro, show that these drugs act specifically on proteins, DNA, and the nucleoproteins of the cell nucleus.¹⁷ The more rapidly proliferating cells are most sensitive to these agents.⁸ This applies to both normal and neoplastic cells. The question arises as to whether or not a drug with such general tissue affinity can be administered in high enough dosage to cause permanent neoplastic regression without prohibitive side effects.

Although complete isolation is technically difficult to achieve, the localized marrow depression together with pelvic nerve damage and radiomimetic skin effect over the external pelvis alone suggest that clinically an acceptable isolation was obtained in the present case and should be generally obtainable. When a number of patients like the present one have been given alkylating agents to the point of major complication and have been followed over a long period of time, an answer regarding cancerocidal effect can be given.

The method employed in perfusing the pelvis of this patient differed only slightly from that advocated by Creech,⁶ Ryan,¹⁵ Stacey,¹⁷ and their associates. They used a large bubble oxygenator and cannulated the aorta and inferior cava directly.⁶ A modified Clowes membrane lung⁵ perfected by Peirce and co-workers¹⁴ was used. The surgical approach to the pelvis was extraperitoneal rather than intra-abdominal. This permitted simple femoral cannulation.

Conclusion

An instance of neurological damage attributed to the toxicity of nitrogen mustard is discussed. This complication occurred following pelvic perfusion with concentrated amounts of the drug for the purpose of treating pelvic neoplasia. Whether this was a direct effect of mustard on nerve tissue or a secondary effect caused by damage to local blood supply was not ascertained.

According to experimental data recorded in the literature the neurotoxicity rather than damage to the bone marrow may be the principal limiting factor to the use of high dosages of nitrogen mustard in perfusion techniques.

Appreciation is expressed to Drs. C. Peirce and H. Dabbs of the Department of Surgery for helping to make the perfusion studies possible.

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Postoperative rupture of major vessels after radical pelvic operation

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IN VIEW of the current incidence of radical operations for advanced pelvic cancer, it is in order to record major complications as they are observed in this field of surgery for the benefit of those interested. Objective evaluation of surgical therapy is possible only if the complications and the limitations of coping with them are emphasized as well as the more satisfactory results.

One of the most dramatic complications of radical pelvic operations is the sudden massive hemorrhage that may occur relatively late in the postoperative course at a time when bleeding no longer is anticipated. Fortunately, this complication would seem to be rare, and in the experience of this service only 12 cases were encountered over the past 12 years among a total of more than 1,500 radical pelvic operations for cancer of the uterus.

Eight patients received total pelvic exenterations, one had anterior pelvic exenteration and 3 had radical excision of a retained cervical stump with pelvic node resection. In all instances, large pelvic packs were inserted at the time of operation and removed usually on the third day.

The sudden massive bleeding usually occurred between the seventh and the ninetieth day following operation and was due to a

From the Memorial Center for Cancer and Allied Diseases.

This study was facilitated by a grant from the James S. and Marvelle W. Adams Foundation, Greenwich, Connecticut. rupture of a major pelvic vessel. In 10 of the 12 cases, this was confirmed by exploratory laparotomy or autopsy. Two cases were unproved but were presumed to be ruptures because of the sudden copious hemorrhage from the vaginal orifice, from which the patient died.

It is interesting that these ruptures involved primarily only large arteries. Four involved the external iliac, 2 the common iliac, 2 the hypogastric, and one the superior gluteal artery. Only one vein, the external iliac, was involved in one patient. Pertinent data on the 12 patients are summarized in Table I.

In evaluating the etiology a number of factors are considered. These included the patient's age, primary diagnosis, previous treatment, type of operation performed, amount of blood administered previously, operative injury to the vessel, the use of pelvic packs, and the presence or absence of postoperative infection. It might be presumed that arteriosclerosis would be a factor in this condition, but such was not the case. Eight of the 10 patients were in their 40's and all had apparently healthy vessels at the time of the initial procedure. Most operations were performed primarily for carcinoma of the cervix or cervical stump but also included were an adenocarcinoma of the rectosigmoid and an adenocarcinoma of the ovary. Seven had received previous x-ray therapy; one had had a total hysterectomy elsewhere for carcinoma of the cervix. The amount of

Table I

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Patient, age, and location of cancer	Previous treatment	Initial operation and units of blood	Pelvic pack removed	Complications of operation	Vessel rupture and day
Y. C.; 54 years; cervix	Radiation	Total pelvic exen- teration; 26 units		Wound infection; pelvic abscess; no culture	Left external iliac artery; nineteenth day
D. S.; 45 years; cervix		Total pelvic exenteration; 11 units	Fourth day	Necrotic colostomy bud; small bowel fistula; nonhemolytic strepto- coccus; enterococci; anaerobic gram-positive rods	Left external iliac artery; tenth day
W. R.; 49 years; stump	Radiation	Excision of cervix stump and pelvic node excision; 4 units	Third day	Pelvic and wound abscesses; Proteus mirabilis; Escherichia coli; Proteus morganii, Streptococcus, hemolytic	Left common iliac artery; seventh day
E. W.; 49 years; stump	None	Excision of cervix stump and pelvic node excision; 14 units	Third day	Bilateral ureteral fistulas; pelvic abscesses; pro- teus; alpha hemolytic streptococcus	Right external iliac vein; seventeenth day
L. L.; 43 years; stump	Radiation	Radical hysterec- tomy and pelvic node excision; 5 units	First day	Left ureteroiliac artery fistulas; pelvic ab- scesses; no cultures made	Left common iliac artery; eighty-first day
S. C.; 48 years; cervix	Radiation	Total pelvic exen- teration; 9 units	Third day	Wound and pelvic ab- scess; no cultures made	Right external iliac ar- tery; eighteenth day
F. S.; 64 years; rectosigmoid	None	Total pelvic exen- teration; 9 units	Third day	Pelvic abscess; E. coli; Proteus; hemolytic en- terococcus	Left hypogastric artery; thirty-fourth day
M. D.; 49 years; ovary	Radiation	Total pelvic exen- teration; 14 units	Third day	Pelvic abscess; Staphylo- coccus aureus hemolyti- cus; enterococcus	
D. J.; 40 years; stump	Radiation	Cutaneous ureter- ostomies; total pelvic exentera- tions; 23 units	Third day	Pelvic abscess; no cul- tures made	Right external iliac artery; eighth day
D. A.; 49 years; cervix	Radiation	Total pelvic exen- teration; 10 units		Pelvic abscess; no cul- tures made	Vessel not identified; twelfth day
G. N.; 50 years; vulva	None	Total pelvic exen- teration and bi- lateral superficial groin dissections	Third day; subsequent repackings	Pelvic infection; P. mirabilis	Vessel not identified; twelfth day
E. C.; 42 years; cervix	Radiation	Anterior pelvic ex- enteration	Second day	Peritonitis; ileovaginal fistula; abscess abdomi- nal wall; Proteus; non- hemolytic staphylococ- cus	

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No. days from pelvic abscess to rupture	Management of rupture	Units blood at second operation	Control of pelvic infection	Status of leg on ligated side	Results after repair	Remarks
6	Repair of per- foration	2 before, 7 during	Yes	Viable; good func- tion	Died; septicemia from buttocks 2 months later	Sutured rupture broke down ninth day re- quiring ligation of artery and 9 addi- tional units of blood
10	Repair of per- foration	5 before, 8 during	No	Color re- turned second day	Died; septicemia; seventh day	Sutured rupture broke down 18 hours re- quiring ligation of artery and 8 addi- tional units of blood
7	Ligation of left common iliac artery	9 blood, 2½ plasma	No	Viable	Died; septicemia; twentieth day	Large and small bowel fistulas requir- ing bowel resection and colostomy
Abscess found at operation for vein ligation	Ligation of right external iliac vein	12	No	Viable	Died; peritonitis; fifteenth day	4 days after vein liga- tion second massive hemorrhage requir- ing ligation of right external iliac artery and 21 units of blood
3	Ligation of left common iliac artery	1 before, 8 during	Yes	Viable; good func- tion	Well 10 years; rib . metastasis	MES .
5	Ligation of right external iliac artery	15 blood, 6 plasma	No	Viable	Died; septicemia; six- teenth day	
15	Ligation of left hypogastric artery	24 blood, 3 plasma	No		Died in operating room of shock	
3					Died of hemorrhage be- fore anything could be done	Autopsy obtained
Abscess found at operation for ligation	Repair of per- foration	5 before, 7 during			Died during operation for ligation	
3					Died in bed	No autopsy
4				1	Died in bed	No autopsy
6	Ligation of right hypogas tric artery	6		Viable	Died of peritonitis 9 days after operation to repair bowel fistula 3 months after exenteration	

blood used at the time of primary operation varied from 4 to 26 pints with most of the cases requiring about 10 pints. This is indicative of difficult dissection and varying degrees of pelvic cellulitis. None of the vessels were injured during the initial operations although all had the overlying peritoneum and surrounding fat tissue and lymph nodes removed. In all instances large pelvic packs were employed and most were removed in 3 days per vaginam. One was removed in one day while another remained in for 6 days owing to oversight since it is usual to remove the packs under Pentothal Sodium anesthesia on the third day. In the latter case, the pack was rather foul smelling at the time of its removal and undoubtedly contributed to the associated infection.

The most apparent, significant etiological factor was one which was present in every case, i.e., severe postoperative pelvic infection. Usually, this was in the form of an abscess which developed 3 to 15 days prior to actual rupture of the vessel. Although the pelvic abscess was drained, a residual, "smoldering" infection seemed to have led to necrosis of the vessel wall. This occurred despite the continual use of antibiotics in large doses. It is routine to give 1 million units of penicillin every 6 hours and 0.5 Gm. of streptomycin twice a day, at least, for 5 days after operation.

Immediate treatment of the massive hemorrhage consisted principally of attempts to control it with packing through the vagina while the blood loss is replaced. The latter required the use of from 9 to 24 pints of blood. In 2 of the 12 patients, hemorrhage was so vigorous as to prove fatal before active therapy could be undertaken. An autopsy was obtained in one, who died before secondary operation, confirming the diagnosis of a ruptured iliac artery. With blood being pumped rapidly through multiple cut-down sites, the patients were taken to the operating room for laparotomy. Two died during the exploratory laparotomy. Of the 7 who survived laparotomy, 5 had either the common or the external iliac artery ligated while 2 had the external iliac artery repaired by suture. In most instances, the wall of the artery was necrotic, making repair unfeasible. This was emphasized by the fact that the 2 that were repaired subsequently ruptured in the same area and required re-exploration and complete ligation of the vessel. One of the repaired arteries held for 9 days while the other broke down in 18 hours. On the basis of this experience, repair of such ruptured vessels should not be attempted; rather, ligation at the time of initial hemorrhage is clearly indicated.

Although satisfactory immediate control of bleeding was achieved in most instances, the end results in these patients were dismal, indeed. All but one patient died of septicemia. The surviving patient was unusual in that the rupture occurred 81 days after the initial operation and was associated with a left ureteroarterial fistula. This was treated in 1949 by ligation of the left external iliac artery and catheterization of the ureter. The latter was subsequently reimplanted into the bladder. At present, this patient is living with normal intravenous pyelograms, but now, 10 years later, she has a rib metastasis from the cervical carcinoma. She is able to walk although the involved leg is noticeably cooler than the other and she does complain of intermittent claudication. One other patient survived long enough for us to ascertain that the leg did not become gangrenous and was functional. However, most of the patients died before the leg could be tested for function by actual walking. In all but one of the patients who died, the pelvic and abdominal infection was not controlled at that time of death. In the one patient, the pelvic infection was controlled but she developed abscesses in the buttocks, probably at the sites of multiple penicillin injections, and she subsequently died of septicemia. Cultures were obtained from 7 patients with varying results. Usually, multiple organisms were recovered and those that seemed to be most prominent included Proteus mirabilis, hemolytic streptococcus (enterococcus type), and Escherichia coli. Staphylococcus was present in only 2 cases. Failure to secure cultures at the time of the ruptures of the 50

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infection, not apparently fulminant, leading to pelvic abscess formation was the principal etiological factor.

Once this series of events occurred, i.e., radical pelvic operation for cancer with node excision in a field of chronic pelvic cellulitis, subsequent abscess formation and then massive pelvic hemorrhage, the prognosis proved grave, indeed, since, if the patients did not succumb from the hemorrhage, they died later of septicemia in all but one instance.

It would appear that the principal treatment is prophylactic to avoid, in so far as possible, postoperative pelvic abscess. Fortunately, this complication is relatively rare.

vessels in 5 cases is ascribed to oversight during the pressure of the acute events.

Summary and conclusions

In 12 patients in whom radical excisions of advanced pelvic cancer by either total or anterior pelvic exenteration or radical excision of the retained cancerous cervical stump with pelvic node excision were carried out, major pelvic vessels were observed to rupture suddenly on the seventh to the ninety-second day postoperatively, causing sudden massive hemorrhage.

It would seem that postoperative pelvic

Sulfamethoxypyridazine (Kynex)—an evaluation in urinary tract infections

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A SATISFACTORY experience with a new sulfonamide, Kynex, on a gynecologicobstetric service will be described. For many years the sulfonamides have had widespread usage in control of infections. It is important to re-evaluate periodically the value of drugs and to compare the old established agents with the new ones. This recent addition to the sulfa family has been under rather intensive investigation.1, 2 The drug has excellent qualities. It is well absorbed from the gastrointestinal tract; it is slowly excreted with minimal conjugation, and it is highly soluble in urine. It maintains a good blood level on a low dosage schedule. The ability of one or two tablets a day to be effective is an attractive feature of the drug. Kynex has much the same absorption, toxicity, body distribution, and excretion properties as other sulfonamides.

Method of study and effects of Kynex

In 1956 a study was begun in the Department of Obstetrics-Gynecology at the University of Miami-Jackson Memorial Hospital to evaluate the efficacy of Kynex in urinary tract infections. All patients treated were chosen without any recognized bias. For purposes of analysis the patients

are divided into three groups: (1) those with cystitis, (2) those with pyelonephritis, and (3) those with indwelling catheters. One hundred seventy-four patients were studied. Of these, 77 had cystitis, 45 had pyelonephritis, and 52 had an indwelling Foley catheter.

Criteria for eligibility to each of the groups were as follows: Cystitis was diagnosed in patients with dysuria, frequency, nocturia, or pyuria greater than 10 white blood cells per high power field; a positive urinary culture might or might not be present. Patients were considered to have pyelonephritis if they had the symptoms of cystitis plus fever, chills, and a positive culture of the urine; many had costovertebral angle tenderness but this was not a requisite. Most of the patients with indwelling Foley catheters were those in the immediate postoperative period following a vaginal hysterectomy with an anterior and posterior repair; the catheters were in position for 2 to 16 days with an average of 5.2 days.

We thought it advantageous to evaluate Kynex in two dosage schedules, so part way through the study the dosage of Kynex was increased. The earlier group of patients (116 patients), referred to as Series A, received 1,000 mg. of Kynex as an initial dose and then 500 mg. (one tablet) daily. The second group of patients (58 patients), Series B, received 2,000 mg. at the begin-

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ning of therapy and then 500 mg. twice daily.

The routine laboratory studies, obtained before and after treatment, included complete blood counts, urinalysis on catheter specimens, aerobic and anaerobic cultures of the urine, and blood sulfa levels by the Bratton-Marshall method, which measures free sulfa. Reticulocyte and platelet counts were done on all patients both before and after treatment. The patients were carefully observed for side effects.

Blood levels. The sulfa levels achieved by the dosage schedules used in this study were adequate. The mean blood level of free sulfa

in Series A (1.0 Gm. of Kynex initially and then 0.5 Gm. daily) was 7.8 mg. per cent with a range of 1.9 to 17.2 mg. per cent. In Series B (2 Gm. of Kynex initially and then 1 Gm. a day) the mean blood levels of free sulfa were 11.7 mg. per cent, ranging between 5.3 and 19.0 mg. per cent.

Toxicity. There have been reports of toxic manifestations from Kynex, as there have been from other sulfonamides. Schwartz and Norton³ reported 2 cases of thrombocytopenia, one of which was associated with leukopenia. Both patients recovered rapidly from the reactions. A generalized allergic reaction was reported by Tisdale⁴

Table I. Results of Kynex therapy in patients with cystitis, pyelonephritis, or an indwelling catheter

					Re	sults			
	No. of cases	E	xcellent	Sa	tisfactory	Uns	atisfactory		Poor
Cystitis									
Series A	47	5	(10.6%)	27	(59.5%)	13	(27.8%)	2	(2.1%)
Series B	30	10	(33.3%)	11	(36.6%)	6	(20%)	3	(10.1%
Pyelonephritis									
Series A	27	4	(14.8%)	14	(51.8%)	8	(29.6%)	1	(3.8%)
Series B	18	2	(11.2%)	8	(44.4%)	7	(38.8%)	1	(5.6%)
Indwelling catheter									
Series A	42	1	(2.4%)	8	(19.1%)	26	(61.9%)	7	(16.6%
Series B	10	1	(10%)	3	(30%)	5	(50%)	1	(10%)

Table II. Organisms and results in treatment of cystitis

	S	eries A	(0.5 Gr	n. daily)		Se	eries B	(1.0 Gm	. daily)	
		Cu	red	Not c	ured		C	ured	Not	cured
Type of organism	No. of patients	Excel- lent		Not satis- factory	Poor	No. of patients	Excel- lent		Not satis- factory	Poor
No growth	18	1	2	11	4	5	-	3	1	1
A. aerogenes	8	-	2	4	2	3	2	1	****	-
E. coli	7	4000	3	2	2	13	5	6	2	-
Proteus vulgaris	3	****	***	3	-	1 .	-	-	1	-
Paracolon	2	***	1	1	-	2	1	-	-	1
E. coli and A. aerogenes	2	_		2	-	2	-	-	2	
E. coli and Enterococcus	1	***	-	1	-	1	-	-	-	1
Alpha streptococcus	1	_	-	1	-	1	1	-	-	-
Staphylococcus albus	1	_		1	-	1	-	1	-	-
Pseudomonas	2		-	2	_	-		-	-	-
Alcaligenes fecalis	1	_	-	1	-		-	-	-	_
Enterococcus	1	-	-	1	-	-	-	-	-	-
Yeast	***	-	-		-	1	1	****	***	-
Summary of results	47	9 "c	ured"	38 "not	cured"	30	21 "	cured"	9 "not	cured"

following a 37 day course of Kynex in which a patient received 1.0 Gm. daily. Four days after the discontinuance of Kynex this patient developed focal hepatitis, fever, and a skin rash.

In our series few toxic manifestations were encountered and they were not serious. One patient developed a typical generalized sulfonamide rash after 6 days of taking 0.5 Gm. Kynex daily, but the laboratory findings were not notable. The rash disappeared in 2 weeks. The one patient who had hematuria soon developed a vesicovaginal fistula due to a malignancy; the platelet and reticulocyte counts were normal, and a toxic reaction was not considered to be present. In only one patient were sulfa crystals reported in the urine and she exhibited no untoward effects. Another patient, who had had a leukocyte count of 6,800 prior to treatment, developed a relative leukopenia of 3,600 per cubic millimeter after taking 1.0 Gm. Kynex daily for 3 days. The drug was not discontinued, and the count returned to a normal range within 3 days without specific treatment.

No evidence of cyanosis, renal damage, or mental aberration was seen during this study. Perhaps the minimal toxic findings can be attributed to the relatively short duration of treatment. Most of the serious side effects reported elsewhere were seen in patients with 4 or more weeks of daily treatment.

Control of infection

The results of treatment were classified as excellent, satisfactory, unsatisfactory, or poor. For a result to be considered excellent, symptoms had to disappear, the pyuria had to clear, and the culture had to be negative. For a satisfactory result, there had to be a very significant decrease in both symptoms and pyuria as well as an improvement in the urinary culture. Results were considered unsatisfactory if only one of the three criteria was improved, and a poor result denoted an actual increase in both symptoms and laboratory findings. Table I combines the results in both Series A and Series B with all classes of patients treated.

Cystitis. Seventy per cent of the patients with cystitis had an excellent or satisfactory response. The results with treatment for various organisms are given in Table II. The most frequent good results in the group of patients with cystitis were obtained when the offending organisms were either Escherichia coli or Aerobacter aerogenes, the most frequently found organisms. This finding is consistent with other studies. The increased dose that the patients in Series B obtained gave a slightly more satisfactory response than did the smaller dosage.

Table III. Organisms and results in treatment of pyelonephritis

	S	eries A	(0.5 G	m. daily))	S	eries B	(1.0 Gn	n. daily)	
		Cı	ired	Not a	ured		Cu	red	Not c	ured
Type of organism	No. of patients	Excel- lent	Satis- factory	Not satis- factory	Poor	No. of patients	Excel- lent	Satis- factory	Not satis- factory	Poor
E. coli	11	1	7	2	1	7	1	5	1	-
A. aerogenes	8	2	2	4	-	2		-	2	-
Alpha streptococcus	2	-	2	-	-	2	1	1	_	-
Staph. aureus	2	1	1		-	0	~~	-		-
Pr. vulgaris	1	-	-	1	-	3	-	-	3	_
Enterococcus	1	***	-	1	-	0	-	-	***	-
Staph. albus	1	-	1	-		1	****	1		_
Paracolon	0	_		-		1	-	1	_	-
Proteus and A. aerogenes	0	-	-		-	1	_		-	1
No initial growth	1		1	_	-	1	-	-	1	-
Summary of results	27	18 "	cured"	9 "not	cured"	18	10 "	cured"	8 "not	cured'

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Table IV. Organisms and results in treatment of patients with indwelling catheter

	S	eries A	(0.5 G	m. daily)		S	eries B	(1.0 Gn	n. daily)	
		Cu	rëd	Not c	ured		Cu	red	Not a	ured
Type of organism	No. of patients	Excel- lent	Satis- factory	Not satis- factory	Poor	No. of patients	Excel- lent	Satis- factory	Not satis- factory	Poor
No growth	18	1	2	11	4	3	-	2	1	_
A. aerogenes	8	-	2	4	2	1	-	-	1	
E. coli	3	-	1	1	1	5	1	1	2	1
Pr. vulgaris	3	_	-	3	-					
Paracolon	2	-	1	1	-					
Staph. albus	2		1	1	-					
Alcaligenes fecalis	2	-	1	1	-					
Pseudomonas	1	-	_	1	-					
Alpha streptococcus	1	-	-	1	-	1	-		1	-
E. coli and A. aerogenes	1	-	-	1	-					
E. coli and Enterococcus	1	-	-	1	****					
Summary of results	42	9 "c	ured"	33 "not	cured"	10	4 "c	ured"	6 "not	cured"

Pyelonephritis. Seventy-seven per cent of the patients on the smaller dosage (Series A) and 56 per cent of those on the larger dosage (Series B) have had excellent or satisfactory results. The results in the treatment of pyelonephritis are detailed in Table III. As in cystitis, *E. coli* and *A. aerogenes* were the most common organisms found in pyelonephritis. There was no significant change in the therapeutic response with the higher dosage in the Series B patients.

Indwelling catheters. For the patients with indwelling catheters the success of the treatment with Kynex had to be defined differently. For an "excellent" or "satisfactory" result the signs and symptoms of an existing urinary tract infection had to disappear, or, if no infection was present at the onset of therapy, the genitourinary system had to remain normal throughout the period of treatment. The labels "unsatisfactory" or "poor" denote either an increase in an existing infection or the appearance of a urinary tract infection during treatment. Kynex proved to be similar to all other antimicrobics in that it failed in many cases to prevent infection as long as the catheter remained in the bladder. Seventynine per cent of Series A and 70 per cent of Series B results were unsatisfactory or poor (Table IV).

Length of treatment. The average length of treatment varied with the indication for treatment. Patients with cystitis received the Kynex for an average of 3.7 days; those with pyelonephritis had an average of 6.7 days of therapy. In the latter group Kynex was discontinued after 4 or 5 days if no improvement was noted. Discontinuance was necessary for 3 patients in Series A and 2 in Series B suffering from pyelonephritis because of the severity of the disease and the lack of response. A. aerogenes and Pr. vulgaris were the organisms involved in the above resistant cases.

In this clinical evaluation of Kynex the drug compared favorably with other sulfonamides in the treatment of urinary infections.5-7 Kass,5 in uncomplicated infections, that is, with only a single organism responsible, found that either sulfanilamide, sulfapyridine, sulfathiazole, or sulfamerazine produced bacteriologic control in 80 to 90 per cent of the patients. However, in complicated infections, that is, chronic cases sometimes with urinary tract abnormalities and a variety of organisms, the bacteriologic control dropped to a range of 17 to 58 per cent. The specific percentage depended upon the sulfonamide used. Although Kass' series and ours are not completely comparable, the 70 per cent satisfactory response in our patients treated with Kynex for relatively uncomplicated infections compares favorably with that of other sulfonamides. In the complicated infections our 60 per cent satisfactory results seems to be a very good response.

Summary and conclusions

One hundred and seventy-four patients on a gynecologic-obstetric service were treated with Kynex and were closely observed. Seventy per cent of the patients with cystitis and 60 per cent of the patients with pyelonephritis had at least a satisfactory response. As anticipated, only 22 per cent of the patients with an indwelling catheter could be proved to have been helped. The toxicity of the drug was low. The maintenance dose was only 0.5 or 1.0 Gm. a day.

The Kynex used in this study was kindly supplied to us by Lederle Laboratories, a Division of American Cyanamid Company, Pearl River, New York.

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OBSTETRICS

Renal function in human pregnancy

IV. The urinary tract "dead space" during normal gestation

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IT IS well known that, during the course of human gestation, certain portions of the urinary tract, notably the ureters and the renal pelves, undergo varying degrees of relaxation and dilatation.^{1, 2} This dilatation, together with the displacement of the bladder imposed by the presenting part, may enlarge the volume of the urinary tract "dead space" which is usually defined as the trajectory through which the urine has to travel from the site of its final assembly in the kidney to the end of a urethral catheter. Estimation of renal clearances would, under these circumstances, involve a sizable error caused by the trapping of a large portion of

urine in the enlarged dead space. Although the alterations in the urinary tract during pregnancy have been qualitatively investigated both radiologically and anatomically, no quantitative determinations of the volume of dead space have been made.

In this study, an attempt was made to measure the changes in the volume of the urinary tract dead space which occur during the course of normal gestation and after delivery. The influence of variation in the rate of urine flow on the volume of the dead space was also investigated. It was hoped that the data might throw light on the magnitude of error incurred in the calculation of renal clearances during pregnancy and at different rates of urine flow.

Material and methods

The studies were carried out on 19 pregnant women of whom 9 were studied once in each of the 3 trimesters of pregnancy and again 6 to 8 weeks post partum. The re-

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This study was supported by grants from the National Heart Institute, National Institutes of Health, United States Public Health Service.

*United States Public Health Service Trainee in reproductive physiology. maining 10 subjects had studies performed once or twice during their pregnancy and occasionally in the postpartum period. Each test was carried out in the hospital in the postabsorptive state in a separate and quiet room with the patient lying in either the supine or the lateral recumbent position. Since most renal clearance studies are usually performed at a rate of urine flow of 1 to 2 ml. per minute, an attempt was made to secure from each subject that was followed throughout pregnancy at least one determination of the dead space volume during each trimester and post partum at a urine flow close to 2 ml. per minute. Other determinations of the dead space volume were made on these and the remaining subjects at urine flow rates which varied between 1 and 10 ml. per minute.

In order to achieve a stable urine flow at a desired level, an equilibration period of 2 to 4 hours was allowed during which a constant infusion of 5 per cent glucose in water was administered and was adjusted frequently according to the rate of urine flow. When several 10 to 20 minute urine collections

showed a stable flow, 600 mg. of sodium para-aminohippurate (PAH) was rapidly injected into one of the antecubital veins. Urine was then collected through an indwelling catheter at 30 second intervals and complete emptying of the bladder was achieved with air wash out.

PAH levels in the urine were determined by the method of Smith and associates.3 Urinary tract dead space was estimated by the method of McSwiney and de Wardener.4 In essence, this method is based on the principle that the delay time (D) which is the time consumed by the urine formed in the kidney to traverse the renal collecting tubules, calyces and pelvis, the ureter, the bladder, and the urethral catheter is related to the dead space volume (X) and the urine flow (V) by the formula $D = \frac{X}{V}$. The urine flow is easily determined. The delay time (D) can be estimated from the time of injection of PAH in the antecubital vein to the first appearance of this substance in the urine. This delay time, of course, includes the armkidney circulation time in addition to the

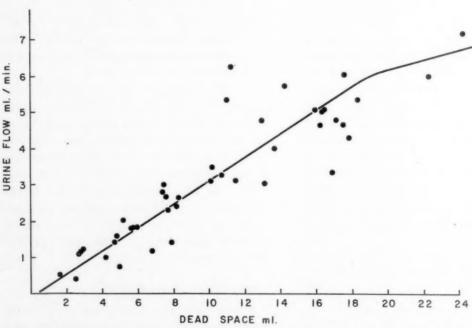


Fig. 1. Relationship between urine flow and the volume of urinary tract dead space. A good correlation exists between these two parameters. The larger the urine flow, the greater is the dead space.

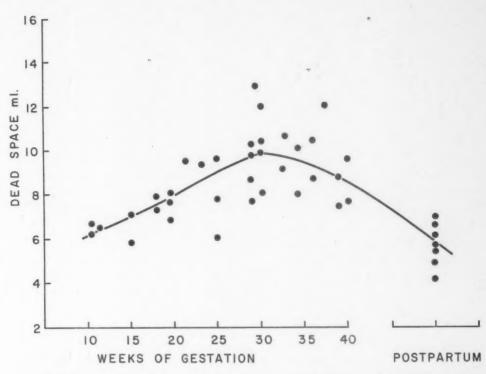


Fig. 2. Changes in the volume of the urinary tract dead space throughout gestation and in the postpartum period. Note that, in general, there is a certain increase in the volume of the dead space during pregnancy with a return to prepregnancy levels after delivery. Note also the marked individual variation which exists in the latter part of pregnancy.

urinary tract delay time. By allowing approximately 15 seconds for the arm-kidney circulation time, the delay time for the urinary tract can be calculated. With the urine flow and the delay time known, the dead space volume (X) is calculated.

Results

A total of 42 tests were completed during pregnancy and after delivery on these 19 subjects. Fig. 1 shows the relationship between the volume of the urinary tract dead space and the rate of urine flow. All figures are corrected to 1.73 M.² of body surface. It can be seen that a very good correlation exists between the volume of the dead space and the urine flow. The larger the urine flow, the greater is the dead space. This finding is in agreement with those of other authors who studied the dead space in animal and man^{5, 6} and was to be expected from the mathematical equation itself.

Fig. 2 illustrates the changes in the volume

of the urinary tract dead space throughout the course of gestation and after delivery. In order to make possible comparison of the volume of the urinary tract dead space among the different subjects studied during pregnancy and post partum, all dead space values were extrapolated to urine flow of 2 ml. per minute and corrected to 1.73 M2 of body surface area. In this way, the urine flow was kept constant while the length of gestation remained as the only variable. It can be seen that a certain increase in the volume of urinary tract dead space occurred between the first and the second trimester of pregnancy (Fig. 2). In both trimesters, the variation from one pregnant subject to another was relatively small. Although in the third trimester the dead space showed a tendency to increase further, the individual variation was extremely large and, in certain instances, the corrected dead space approached 13 ml., which was twice the average value of the first trimester. During the postpartum period, the values for the dead space returned to the prepregnancy level, which is below 6 ml.

Comment

It is estimated that approximately 80 per cent of pregnant women have demonstrable hydroureter which is more frequent on the right side than on the left.2,7 The cause of this dilatation is not well established. Mechanical and functional factors are believed to be operating. The fact that the dilatation of the ureter may be observed as early as the fourth month of gestation speaks against the mechanical effects of the enlarged uterus as being the only cause and suggests strongly that hormonal factors may be the predominant ones. If this were true, other portions of the urinary tract such as the renal collecting tubules, the renal pelvis, and the urinary bladder may also undergo a certain relaxation and dilatation, thereby enlarging the over-all urinary tract dead space.

The present data show that the volume of the urinary tract dead space increases throughout the course of gestation and returns to prepregnancy levels during the postpartum period. The wide spread in the individual values which exists in the third trimester of gestation points to the difficulties of assessing the volume of the dead space in a given subject. This problem becomes pertinent when renal clearance studies in pregnancy are evaluated, particularly in the third trimester. It is axiomatic that the accuracy of renal clearance determinations is strictly dependent on complete urine collections. If the volume of the dead space is too large, a portion of the urine may remain trapped and may not be collected until the following clearance period. Thus, an error is introduced in the estimation of the clearance of the substance under study. This error is magnified considerably when the urine flow is below 1 ml. per minute. Although the volume of the dead space is smaller when the urine flow is low, the fraction of urine trapped becomes relatively important since it may represent a sizable portion of the urine flow included in the calculation of the renal clearance. This problem is aggravated by the fact recently demonstrated by Levinsky and Berliner⁸ that at low rates of urine flow and particularly in an enlarged dead space the diffusion of water and solutes through the urinary tract membranes becomes accelerated. All these factors seem to indicate that in studying renal function during pregnancy, extreme care should be given to the rate of urine flow and to the magnitude of error incurred from the size of the dead space. These multiple causes of errors probably account for some spurious data which have been reported on the clearances of inulin and PAH during pregnancy. De Alvarez9 claimed the presence of an unexplained fall in glomerular filtration rate and renal plasma flow in the last trimester of pregnancy. This finding was certainly contrary to that of all other investigators. 10-12 Furthermore, the fall found by this author coincided with the peak of cardiac output increase in pregnancy and, therefore, it can be explained only on the basis of an active renal vasoconstriction. On physiological grounds, this seems untenable since there is no indication that the kidneys undergo a spontaneous vasoconstriction in the latter part of gestation. Although the data published by this author did not contain individual values of urine flow, there seems to be an indication that his average value was approximately 0.9 ml. per minute. This low urine flow may certainly account for the low clearances observed by this author in the last trimester of pregnancy.

The same cause of errors might have been operating in our results on the effects of Pitressin on renal hemodynamics and electrolyte excretion in the latter part of pregnancy. A fall in renal hemodynamics occurred in every case after the administration of Pitressin prior to delivery. Such a finding was contrary to the usual action of this hormone in the nonpregnant state. Here again, the marked fall in urine flow induced by Pitressin might have played a part in this unusual action. This problem has been discussed in detail elsewhere. 18

Summary and conclusions

1. Urinary tract dead space was measured during normal human pregnancy and after delivery.

2. A progressive increase in the volume of the urinary tract dead space occurs throughout gestation. In the third trimester, a marked individual variation exists which makes it extremely difficult to assess the volume of the dead space in a given patient.

3. These changes have been discussed in terms of their influence on the calculation of renal clearances during pregnancy.

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Alterations in liver function during normal pregnancy

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The occasional occurrence of abnormal results in liver function studies performed on pregnant women with no obvious clinical symptoms of liver disease during their pregnancy raised the question, "Can the usual laboratory normal values be used as the standard for interpretation of liver function studies in pregnant women?" Some of the more commonly used liver function tests were studied in normal pregnant women throughout the course of their pregnancy as an index of the degree to which liver function is disturbed during pregnancy and to establish so-called "normal" values for these tests in pregnancy.

This paper describes the results of studies performed on over 600 normal pregnant women during pregnancy and during labor. Blood was drawn from approximately 300 of these patients on admission to the labor rooms. Thirty patients were followed at approximately monthly intervals beginning with their first visit to the obstetrician. In the remainder of the patients, blood was drawn once or occasionally twice during pregnancy. The majority of these patients were from the middle class income group with the remainder about evenly divided between upper and lower income groups. The obstetricians were not informed of the results and only the usual obstetrical care was given these patients. No patient with a history of liver disease was included in this study and none of the patients developed any clinical symptoms of liver disease during the investigation.

Methods and results

The tests used include cephalin cholesterol flocculation, 10 thymol turbidity, 12 total cholesterol and cholesterol esters, 1 bilirubin, 13 total protein and albumin-globulin ratio, 16 and alkaline phosphatase. 8 In addition to the pregnant patients a small series of blood donors and medical technologists were simultaneously studied for direct comparison. The majority of the blood donors were healthy young males in the same age group as the patients. There were no professional donors. The female technologists were not pregnant and were in the same age group.

A. Cephalin cholesterol flocculation. The average cephalin flocculation was negative in 24 hours throughout the course of pregnancy and there was no consistent increase in the percentage of patients with more than 1-plus cephalin flocculation from the beginning of pregnancy until near term (Table I). However, from 8 to 12 per cent of pregnant women have a 2-plus or greater flocculation at or near term. Twenty-nine patients with increased cephalin flocculation at term were studied again 4 days post partum. It is interesting to note that in 24 of these there was marked improvement in the cephalin flocculation within 4 days after delivery; 4

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patients showed no change, and in one patient there was an increased flocculation. These and similar findings with the thymol turbidity test would indicate that most pregnant women in whom these tests are abnormal at or near term have no significant liver damage. Day and co-workers3 reported abnormal cephalin flocculation in 22.5 per cent of pregnant women and Salmon and Richman¹⁵ found 35 per cent of their series had 2-plus flocculation at term. However, Wetstone and associates17 found between 10 and 15 per cent abnormal results in their cases, which is in agreement with our results.

B. Thymol turbidity. The average thymol turbidity remains within the normal range throughout pregnancy, although a slight but definite rise is seen, particularly in the last trimester. In the first and second trimesters, the average thymol turbidity was 2.5 units. This increased in the last trimester until it was 3.3 units at term. There was a definite increase in the percentage of patients with values above 5 units beginning at the seventh month. During the first 2 trimesters, approximately 6 per cent had an abnormal thymol turbidity level, a value similar to the 8 per cent of donors in whom slightly elevated levels were found; but in the third trimester 15 to 16 per cent of the patients had a thymol turbidity level of more than 5 units (Table I). Dieckmann⁵ also found a slight

rise in thymol turbidity during pregnancy and 16 per cent of his patients had an elevated thymol in the third trimester. However, he reported 15 per cent of his patients had an elevated thymol turbidity level in the first 2 trimesters as compared to only 6 per cent in the present study.6 This figure suggests to us that an elevated thymol turbidity level in pregnancy may warrant more careful investigation than a similar elevation occuring late in pregnancy.

Twenty-four patients who had elevated thymol turbidity levels while in labor were studied again 4 or 5 days post partum. Twelve patients returned to normal range, 10 others had a decrease in thymol turbidity, and 2 did not improve.

The increase in the average thymol turbidity of the technologists group is felt to reflect their increased potential for subclinical hepatitis due to the nature of their work and thus is not representative of other normal nonpregnant females. Since the thymol turbidity test is a more sensitive indicator of homologous serum jaundice or infectious hepatitis than the other tests in these series, this difference would not be expected to be observed in the other tests and it was not.

C. Total cholesterol and cholesterol esters. Increased cholesterol levels in normal pregnancy have been reported previously. The mean elevation has been variously reported

Table I. Occurrence of abnormal liver function tests in pregnant women (per cent of cases)

Duration of pregnancy (months)	No. cases	Cephalin choles- terol floccula- tion >+	Thymol turbidity > 5 units	Bilirubin > 1 mg.	Total protein < 6 Gm.	A/G < 1.0	Choles- terol > 250 mg. %	Alkaline phosphatase > 5 units
1	3	0	0	0	0 .	0	0	
2	14-15	21	6	13	7	0	0	
3	45-50	2	6	8	19	0	0	
4	43-47	2	6	5	23	2	9	
5	29-32	7	6	3	25	3	19	
6	34-37	0	5	3	29	3	53	6 (17 cases)
7	30-36	6	16	7	29	0	55	26 (18 cases)
8	49-54	12	15	4	43	2	57	42 (38 cases)
Term	301-306	8	15	3	20	0	21	
Donors	28-41	2	8	. 0	0	0	0	
Technologists	10-12	0	16	0	0	0	0	

as from 10 to 50 to 100 per cent. The peak elevation has been reported as occurring at about the thirtieth week of pregnancy, in the last trimester, and at the time of labor.9, 14, 17 The percentage of cholesterol esters has been reported as increasing, as decreasing, and as normal.2 Table I shows that the average total cholesterol levels begin increasing during the fourth month of pregnancy, at which time 9 per cent of the patients had cholesterol values over 250 mg. per cent. The cholesterol levels continued to increase through the eighth month at which time 57 per cent of the patients had cholesterol levels above 250 mg. per cent. However, between the eighth month and term these levels decreased markedly. Although the term patients' average cholesterol was still 241 mg. per cent compared to an average of 160 mg. per cent at the end of the first trimester, only 21 per cent of the patients had cholesterol levels above 250 mg. per cent. The donors averaged 162 mg. and the technologists 168 mg. cholesterol per 100 ml. serum. The peak cholesterol elevation occurs during the last trimester and a return toward normal values has already begun before the time of labor. The average cholesterol level increases approximately 60 per cent before reaching its peak, but the individual variation covers a wide range as was seen in the patients on whom serial determinations were made.

Cholesterol ester determinations were made on blood from 181 patients at the time of labor. The average cholesterol ester was 73 per cent of the total cholesterol. Eight patients had less than 60 per cent cholesterol in the ester form and 36 patients had over 80 per cent cholesterol in the ester form. Thus at term, 20 per cent of the patients had an increase in the ester fraction relative to the total, and 21 per cent of the patients still had a total cholesterol level above the usual normal range. Unfortunately, no studies were made of the esters over the period of the greatest increase in the total cholesterol.

D. Bilirubin. Serum bilirubin has been described as being elevated¹¹ and as being normal¹⁷ during normal pregnancy. In the pres-

ent series bilirubin values above 1 mg. per cent were observed in 24 of 564 patients. No values 2 mg. per cent or higher were observed. There were no consistent or significant differences in the monthly averages. Bilirubin values are within the usual range in normal pregnancy.

E. Total proteins and albumin-globulin ratio. The concentration of total plasma proteins gradually falls during pregnancy and our results as seen in Table I further confirm the results reported by many investigators.3, 7, 17, 18 It has been reported that this gradual fall is only relative, however, and is associated with the gradually increasing blood volume and plasma dilution that occurs during the first 7 months of pregnancy.7, 18 The absolute amount of total protein in the circulating blood is increased; Dieckmann⁴ placed this increase at approximately 18 per cent at term. The number of patients who had less than 6 Gm. per cent total plasma protein rose from 7 per cent in the second month to 43 per cent in the eighth month. This figure fell to 20 per cent at the onset of labor (Table I). This corresponds to the gradual increase of blood volume to about the thirtieth week and the gradual decrease until term. A change in the protein fractions was shown by a decreased albumin to globulin ratio. During the third month of pregnancy the average ratio was 2.1. The maximum decrease had occurred by the fifth month at which time the average ratio was 1.7 and the ratio did not return to normal at the time of labor. Both donors and technologists had an average ratio of 2.3. The average albumin to globulin ratio remains well within the normal range, however, and any reversal of the ratio in a pregnant patient should be reason for further investiga-

F. Alkaline phosphatase. Although the alkaline phosphatase levels were determined in only 91 patients, a marked increase in activity may be seen in the third trimester. During the eighth month 42 per cent of 38 patients had values above the usual normal (Table I). This confirms the reports of others^{11, 17} and further demonstrates that eleva-

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Table II. Abnormal liver function tests in multipara and primipara at term

	Primit	para	Multif	para
Test	Average	% abnormal	Average	% abnormal
Cholesterol	206 mg. %	11	218 mg. %	24
Thymol turbidity	3.0 units	10	3.5 units	21
Cephalin cholesterol				
flocculation	Negative	7	Negative	9
Bilirubin	0.4 mg.%	5	0.4 mg. %	3
Total protein	6.6 Gm. %	10.8	6.4 Gm. %	21
A/G	1.7	0	1.7	0

tion of alkaline phosphatase activity late in pregnancy without hyperbilirubinemia does not indicate pathologic biliary or extrahepatic obstruction. However, elevation of the alkaline phosphatase activity seen early in pregnancy is probably not due to the pregnancy per se.

To determine whether multiparity increases the abnormalities of the liver function tests, thus indicating some real and permanent effect of pregnancy on the liver, the values obtained in multipara at term were compared with those found in primipara. The multiparous patients ranged from

gravida ii to gravida x. The results may be seen in Table II. Although no data was kept on the patients' ages it is assumed that on the average the multiparous patients were 5 to 10 years older than the primiparas. This age difference might be considered a contributing factor in any small differences and results between the two groups, but any marked differences could not be attributed to it.

It is obvious from Table II that in those areas where pregnancy appears to be exerting an influence (that is, cholesterol, thymol turbidity, and total protein), the multiparous

Table III. Liver function tests during pregnancy*

Date	Thymol turbidity	chol	halin esterol ulation	Cholesterol	Total protein	A/G	Bilirubin
June 10	1.6	-	_	150	8.8	1.8	0.5
July 18	1.7	-	-	200	6.8	1.6	0.5
August 22	1.7	-	-		7.1	1.7	0.2
September 26	2.0	_	-	273	7.6	1.6	1.0
October 31	4.0	+	++	288	6.9	1.4	0.7
December 5	1.8	_	<u>+</u>	250	7.1	1.5	0.0

*Patient M. H.; estimated date of confinement, December 12.

Table IV. Liver function tests during pregnancy*

Date	Thymol turbidity	chol	halin esterol ulation	Cholesterol	. Total protein	A/G	Bilirubin
June 4	2.0	_	-	153	6.7	2.3	0.2
June 27	2.1	-	+	120	6.3	1.9	0.4
July 25	2.9	-	+	215	6.4	1.6	0.2
August 22	2.8	400	-	252	5.7	1.4	0.3
September 26	2.1	_	-		6.6	1.8	0.5
November 7	3.6	-	-	280	6.3	1.8	0.3
November 21	6.4	++	++	302	6.4	2.0	0.6
December 5	3.0	****	ense	275	6.4	1.8	0.5

*Patient E. K.; estimated date of confinement, December 13.

patients show the greatest variance from the accepted norms. Eleven per cent of the primiparas at term still retain an elevated blood cholesterol level whereas 24 per cent of the multiparas at term have an elevated blood cholesterol level. Furthermore, the thymol turbidity was increased in 10 per cent of the primiparous and in 21 per cent of multiparous patients; 10.8 per cent of the primiparas and 21 per cent of the multiparas had less than 6 Gm. per cent of total protein at term.

To determine whether the progressive changes in the liver function tests which are seen to occur in the group are as consistent in the individual, serial determinations were done on 30 patients. Data on 2 of these patients are seen in Tables III and IV. It should be noted that hematocrit determinations were not done and the patients were not fasting in most instances. The values for the individual patients varied from month to month and in the majority of them no consistent monthly increase or decrease was found in any of the tests studied. Nonetheless, many of the patients did have definite, albeit irregular, increases in the thymol turbidity and total cholesterol during the study with a decrease in the total protein and A/G ratio.

Comment

There has been considerable research directed toward finding changes in liver function during pregnancy which could be used to predict the occurrence of toxemia. However, the changes which occur in liver function during normal pregnancy have not been well established.

With the exception of the plasma cholesterol concentration, the average values for the liver function tests remain within the usual normal limits during pregnancy. However, the number of individuals in whom the liver function tests give values outside these normal limits increases during pregnancy, beginning generally in the second trimester and increasing until near the end of the third trimester. Abnormal liver function, occurring early in pregnancy, as revealed by

the usual tests, warrants further investigation into the possibility of liver disease. The same abnormal test results occurring late in pregnancy without clinical symptoms of liver disease are probably the result of the pregnancy. Elevation of cholesterol levels occurs in such a high percentage of pregnancies as to be considered normal for pregnant women.

Further evidence that liver function is affected by pregnancy is shown by the increased number of abnormal test results in the multiparous patient when compared to those in the primiparous patients.

The rapid return toward normal levels after delivery seen in the majority of patients with abnormal cephalin flocculation and thymol turbidity test findings suggests that the disturbance in liver function does not result from primary parenchymal cell damage but is the result of the external obstruction to the liver or biliary tree which occurs in pregnancy as a result of the increase in intraabdominal pressure. This hypothesis is further supported by the rise in alkaline phosphatase and plasma cholesterol levels during pregnancy. However, the fact that the bilirubin levels do not increase indicates there is no major obstruction to the bile flow sufficient to be the sole cause of the marked increase in the phosphatase and cholesterol levels. This latter may be the result of the changing steroid metabolism accompanying pregnancy and be only slightly influenced by the changes in liver function.

Summary

Liver function studies were made of 600 normal pregnant women during pregnancy and during labor. During the first trimester, values for liver function studies do not differ markedly from those in the general population.

The cephalin cholesterol flocculation is increased near or at term in 8 to 12 per cent of pregnant women. In the third trimester approximately 15 per cent of the patients show an elevated serum thymol turbidity level.

The total serum cholesterol begins to in-

crease at the end of the third trimester. By the eighth month of pregnancy over 50 per cent of the patients have serum cholesterol levels over 250 mg. per 100 ml. of serum. These levels decrease before term.

The serum bilirubin remains within the

usual normal range during pregnancy. The total protein concentration decreases as does the albumin to globulin ratio. However, the latter is normally not reversed. The alkaline phosphatase level increases in the third trimester.

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Vibrio fetus—a cause of human abortion

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AN ORGANISM identified as Vibrio fetus was isolated from a mother and a dead fetus at Charity Hospital in New Orleans. This was found in the course of a study on listeriosis which is being pursued by the Division of Bacteriology of the Department of Pathology.

V. fetus, long recognized as an animal infection, ¹³ was first noted in the United States in 1918 by Smith, ¹² who isolated this organism from the fetuses of 14 cows that had aborted. He established that the death of the fetus resulted from the interference with the placental circulation.

Vibriosis has been classified as the number one enemy of bovine reproduction by Easter-brooks and his associates.⁵ They stressed that a presumptive clinical diagnosis should always be confirmed bacteriologically and serologically. The organism must be isolated from the fetus as well as from the cow in order for its significance to be established, because nonpathogenic vibrios are commonly present in the bovine genital tract.

Curtis⁴ may have been the first to recognize vibrios as a possible cause of human abortion. The first of his two patients had an infection which followed instrumental abortion. Direct smears showed an over-

whelming flora of curved, gram-negative rods, but the organisms could not be classified because they did not grow in the cultures made. The etiological agent of the second infection obtained in pure culture was undoubtedly a vibrio but, as it grew only anaerobically, it was not a V. fetus. Curtis pointed out the need for a study of this group to determine its importance in pelvic infections.

King⁷ summarized 15 of the 17 *V. fetus* infections in humans that have been reported in world literature. Three of these, all reported from France, were associated with problems of pregnancy, 2 of which caused abortion while the third was controlled after extensive treatment and the mother was delivered of a living child at term.

Epidemiology

Vibriosis of animals has been intensively studied. It is believed that the infection may be acquired in three ways: (1) by coitus, (2) by contact with infected animal tissues, and (3) by contamination of food or water.

1. Coitus. Ristic and co-workers⁹ established the first premise experimentally. When nonpregnant guinea pigs were infected intravaginally and housed with noninfected males and females, the control females became infected with *V. fetus*. Ristic and associates¹⁰ also demonstrated that 4 of 9 bovine strains of *V. fetus* inoculated intraperitoneally into male hamsters produced infection in the testes. This experiment showed that the organism has a definite predilection to become established in the genital tract.

V. fetus has been isolated from the semen of apparently healthy bulls. 11 That this or-

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ganism has not been recovered from cows until after the first or second pregnancy^{11, 12} indicates that the male animal acquires the infection and transmits it sexually to the female. Although Easterbrooks and coworkers⁵ classify *V. fetus* as the number one enemy of bovine reproduction, they believe that the infection tends to be transient or even self-limiting in cows, but remains in the bull indefinitely.

Contact with infected animal tissue. Contact transmission apparently takes place but has not been experimentally demonstrated.

The best evidence probably is furnished by Ward, 14 who reported that V. fetus was isolated from a pustule on the face of a person conducting research on this organism. Spink 13 reported V. fetus septicemia in a man who worked on the killing line of a meat-packing plant. Presumably, the infection was acquired by direct contact with infected blood.

3. Contamination of food or water. Guinea pigs have been infected both vaginally and by the gastrointestinal route.¹¹ The fact that agglutination titers were higher in the gastrointestinally infected animals is interpreted as meaning that the uterine infection is localized and does not stimulate high antibody titers.

Case Report

A. B. (T43-81617), a 37-year-old gravida x, para vi, Negro woman was admitted to the Tulane Obstetrical Service at Charity Hospital on Nov. 12, 1958. She gave a history of lower abdominal cramps, spotting, chills and fever, dysuria, nausea and vomiting, and anorexia for the previous 2 days. Her last menstrual period was May 13, 1958, and the expected date of delivery was Feb. 20, 1959. She had felt fetal movement until 2 days prior to admission. She had not attended the prenatal clinic. Except for the fourth pregnancy in 1945, which she aborted at 2 months, her first 6 pregnancies were culminated successfully in the delivery of live, fullterm infants. During the seventh pregnancy, in 1948, she was admitted to the hospital at 5 months' gestation because of anemia of undetermined cause and was treated with whole blood. One month later, she was delivered of a macerated stillborn infant. The eighth pregnancy, 4 years later (1952), culminated in the birth of a 7 month macerated stillborn infant. In 1955 she was admitted with pre-eclampsia and abruptio placentae involving half of the placenta, and was delivered of a living 4½ pound infant by cesarean section. There was no history of other hospitalization or operative procedures.

This patient lived in the metropolitan area with city water and toilet facilities. She denied any contact with aborting livestock or any other farm animals on retrospective questioning.

Physical examination revealed an acutely ill Negro woman. The blood pressure was 110/60, pulse 113, respiration 24, and temperature 104° F. Positive findings were limited to a uterus the size of a 6 months' gestation and a profuse, thick, milky white vaginal discharge. No fetal heart tones were heard.

Laboratory procedures including blood chemistry determinations, heterophil and febrile agglutinations, sickle cell preparations, bleeding and clotting times, serologic test for syphilis, and cultures of the vagina, cervix, and blood were carried out at the time of admission. These were all negative or within normal limits except for 2-plus acetonuria and a white blood cell count of 15,500, 80 per cent of which were polymorphonuclear leukocytes.

Penicillin, streptomycin, and oxytetracycline were administered. Nine hours after admission, the blood pressure was 80/60, pulse 120, and temperature 105° F. A transient rise in blood pressure resulted when 200 ml. of 3 per cent normal saline was given. Chloramphenicol was added to the regimen. Four hours later steroids were added. Physical examination at this time revealed an irritable uterus and a ripe, 2 cm. dilated cervix. Amnionotomy was performed, and a thick, foul-smelling fluid escaped. Clinical impressions at this time were: (1) 6 months' intrauterine pregnancy with fetal death, (2) amnionitis, (3) pyelonephritis, and (4) bacteremic shock. Levarterenol bitartrate* was begun and an intravenous Pitocin drip started. One unit of packed red blood cells was given. Following 21/2 hours of Pitocin augmentation, a 470 gram macerated infant was spontaneously delivered. The uterus was manually explored and found to be intact. Cultures of the placental tissue and fetal brain were made. Steroids and

^{*}Levophed, Winthrop Laboratories, New York, New York.

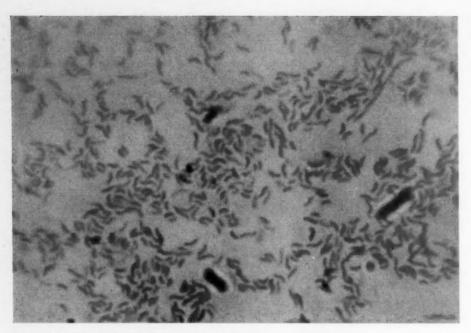


Fig. 1. Vibrio fetus (K106) isolated from the brain of the fetus.

Levophed were discontinued 4 hours post partum. Temperature was then 99.4° F., pulse 85, and blood pressure 105/70.

The patient's urinary output remained adequate throughout the entire hospital course. Antibiotics were discontinued on the sixth postpartum day, and the patient was discharged on the eighth.

The patient was seen at 6 weeks and again at 2½ months for routine postpartum examinations. There has been no history of further illness. Cultures of throat, cervix, and vagina were taken, and blood for serologic studies was drawn on the last visit.

The patient's husband, a 39-year-old Negro merchant seaman, has lived in the city most of his adult life. Several years previously he worked on a ship which transported cows to and from various North and South American ports. He witnessed cows aborting on board but denied contact or handling of these animals. Blood, semen, and culture of the prepuce were obtained on two different occasions.

Laboratory studies. Cultures of the placenta and of the brain of the fetus were made at delivery in brain-heart infusion agar and taken directly to the laboratory. Gram stains were negative after 18 hours' incubation but at 48 hours showed small (1.5 to 2μ by 0.2 to 0.3μ), curved, delicately staining, gram-negative rods (Figs. 1 and 2).

Duplicate subcultures on chocolate agar and blood agar plates were incubated under normal atmospheric tension and anaerobically in the hydrogen jar. Growth was very sparse after 48 hours. Following the suggestion of Bergey,1 fresh plates were inoculated and placed in an atmosphere of increased nitrogen content. A somewhat mucoid growth described by Bryner⁸ was obtained and was subsequently reproduced by incubation under the CO2 tension of the candle jar. Growth without fermentation or gas production took place in lactose, dextrose, sucrose, mannite, xylose, rhamnose, and maltose. Indole was not produced, citrate was not utilized, urea was not split, and hydrogen sulfide was not produced, but the catalase test was positive. This gave presumptive evidence that the organism was V. fetus.2, 8

Both cultures were sent to Miss Elizabeth King of the United States Public Health Service Communicable Disease Center of Chamblee, Georgia, who confirmed the identity of the organisms culturally and serologically. The organism from the mother (K107) agglutinated to a 1:1,280 titer and that from the fetus (K106) to 1:2,560 with specific V. fetus antiserum.

Cultures from the throat, vagina, and cervix were taken $2\frac{1}{2}$ months later when the patient returned on Jan. 30, 1959, for medical evaluation. Only the cervical culture (Y71) showed the presence of V. fetus (Fig. 3).



Fig. 2. Vibrio fetus (K107) isolated from the placenta.

Vibrio fetus organisms have been isolated from the prepuce and semen of infected bulls¹¹ that have transmitted the infection to cows. Such cultures were therefore made from the patient's husband at two different times in an effort to determine a possible source of infection. No vibrios were isolated. Antigens were prepared from the two organisms isolated at the time of delivery following the technique of Ristic and associates. Agglutinations were carried out with the serum taken from the mother on Jan. 30, 1959, and from the husband on Feb. 25, 1959. The results are shown in Table I.



Fig. 3. Vibrio fetus (Y71) isolated from the cervix 21/2 months after delivery.

Table I. Agglutinations

					Serum	diluti	ons			
Antigens	10	20	40	80	160	320	640	1,280	2,560	Contro
Mother's serum									-	
K106 (fetus)	+	+	+	+	+	+	+	-	_	-
K107 (mother)	+	+	+	+	+	+	±	-	-	-
Father's serum										
K106 (fetus)	-	-	+	+	+	+	±	_	-	_
K107 (mother)	+	+	+	+	±	±	-	-	-	-
Control pooled serum										
K106 (fetus)	-	_	-	_	-	-	-	_	-	-
K107 (mother)	-	-	-	-	-	-	-		-	-

Comment

Vibrio fetus has been largely ignored as a cause of human abortion or premature birth, yet it is known to be a common offender in the animal world. Several explanations are possible: (1) perhaps V. fetus is rarely a human pathogen, (2) the organisms, which are very fastidious in their growth requirements, may fail to grow in the culture media with techniques usually employed, (3) the organisms may be only intermittently present in the genital tract so are not often isolated. Veterinarian bacteriologists have been most successful in isolating V. fetus from infected cows if the cultures are made during the estrus cycle.¹¹

The pattern of the infected male transmitting V. fetus sexually to the female with resultant abortion is well-recognized by veterinarians. As the patient had had 4 consecutive pregnancies terminate in abortion or premature delivery, two attempts were made to isolate the organism from the semen and prepuce of the husband. This was not successful, but the possibility of their presence was not ruled out as it is extremely difficult to isolate these fastidious organisms from contaminated material. The fact that the cultures were made 31/2 and 61/2 months after the abortion was not significant if the human infection follows the pattern known to occur in animals. The bull apparently maintains the organism in the testes indefinitely.14

Agglutinations made with the serum of the husband against the organisms isolated from

the mother and the fetus showed definite elevation in antibody titer. The clinical history of repeated abortion together with evidence of antibodies against V. fetus in the blood of the father does not furnish proof but certainly presents presumptive evidence that he has a latent vibrio infection which is transmitted to his wife with resultant abortion.

Summary

- 1. A case of human spontaneous abortion caused by V. fetus infection is described.
- 2. The organism was isolated from the placenta of the mother and from the brain of the fetus.
- 3. Cultural and serologic studies identified the organism as V. fetus.
- 4. Agglutinations showed an elevation of *V. fetus* antibodies in the blood of both the mother and the father.
- 5. Sixteen of the 17 cases of *V. fetus* infection previously reported were associated with septicemia. Three of these reports, all in the French literature, describe accompanying problems of pregnancy.
- 6. We believe this represents the eighteenth case of V. fetus infection in a human being and the first one involving problems of pregnancy recognized in the Western Hemisphere.

Appreciation is extended to Dr. Robert L. Simmons for the photography and to Dr. E. S. Moss and Dr. Conrad Collins for editing the manuscript.

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Pathologic physiology and treatment of postabortal Clostridium welchii sepsis

Report of survival of a patient with massive hemolysis and anuria

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Of the many complications of criminal abortion, Clostridium welchii septicemia stands among the most serious. Death may result in these cases from sepsis, renal failure, or the hematologic and systemic complications of Cl. welchii infection.

Today, the management of postabortal gas gangrene and its complications has progressed to the point where recovery is possible even in an extremely severe case. Such a case, that of a patient who survived postabortal *Cl. welchii* septicemia with massive intravascular hemolysis and anuria, is described in this report.

A 22-year-old unmarried Negro woman was admitted to the emergency room at the Jackson Memorial Hospital on Dec. 7, 1956, for psychiatric evaluation. The patient was having hallucinations and was irrational. No history was obtainable, but a temperature of 105.6° F. and scleral icterus made a diagnosis of physical illness immediately obvious. The pulse was 90 to 120 per minute and the blood pressure 90/60; the patient looked acutely ill. The abdomen was soft but with slight voluntary guarding. Generalized abdominal tenderness with rebound tenderness was present and was greatest in the lower quadrants. Bowel sounds were active.

A speculum examination revealed a foul smelling, bloody discharge in the vagina. No vaginal laceration or other evidence of instrumentation was detected. The cervical os was widely dilated and filled with brownish red necrotic material. The uterus was enlarged to the size of 12 weeks' gestation and was soft and tender. The adnexa were tender but no masses were detected. Bubbles were noted to be exuding from the uterus after removal of the necrotic tissue from the cervical os.

Because of this finding, it was decided to completely evacuate the uterus with ring forceps without delay. A moderate amount of necrotic placenta-like tissue was recovered, accompanied by the release of a large number of frothy bubbles. Rectal examination was negative except for causing referred abdominal pain. Cul-de-sac aspiration produced 3 ml. of pink serous fluid. Neurological examination was unrevealing. There was no complaint of muscle tenderness. Catheterization of the urinary bladder yielded 40 ml. of cola-colored urine.

Laboratory studies on admission. The hemoglobin level was 9.0 Gm. per 100 ml. (serum hemolyzed); hematocrit determination, 14 per cent; white blood count, 32,000 with 64 mature and 25 immature polymorphonuclear leukocytes, 10 lymphocytes, and 1 monocyte. Five nucleated red blood cells per high power field and numerous spherocytes were seen. Urinalysis revealed a specific gravity of 1.018, pH 7.5, albumin 4,500 mg. per liter, sugar and acetone negative, red blood cells 4 to 6 per high power field, white blood cells 6 to 9 per high power field, a rare granular cast and many hematin crystals. Urine guaiac was 4-plus; bacteria 3-plus. The

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*National Institutes of Health Research

serum bilirubin was 0.10 mg. per 100 ml. direct, 1.98 mg. per 100 ml. indirect. The serum sodium was 130 mEq. per liter; the serum potassium hemolyzed; chloride 100 mEq. per liter; carbon dioxide 15.5 mEq. per liter. The clotting time was 15 minutes (Lee-White); clot retraction began in one hour and was complete within 24 hours. An electrocardiogram was within normal limits. Chest x-ray examination and x-ray film of the abdomen were normal. Cl. welchii organisms grew in cultures of the blood, urine, cul-de-sac, and uterine cavity. Subsequent cultures of urine and blood did not grow out Clostridia.

Course on admission. A presumptive diagnosis of septic abortion with Cl. welchii endometritis and septicemia was made on admission. The patient was given one million units of aqueous penicillin intramuscularly, followed by 10,000 units of tetanus antitoxin and 20 ml. of polyvalent gas-gangrene antitoxin intramuscularly in divided doses. An additional one million units of penicillin was given intravenously with 500 ml. of whole blood. Pitocin, 0.5 ml., was given intramuscularly every 4 hours. Within 12 hours fever defervesced to a temperature of 101.6° F. and the patient returned to a rational state. Complete emptying of the uterus was confirmed by pelvic examination, and curettage was deemed unnecessary.

For the first time an adequate history could be obtained. The patient had last menstruated 5½ months previously. Five days prior to admission she visited a midwife who passed a long rag into the patient's uterus without any sterile precautions. Having fallen out after one day, the same rag was reinserted by the midwife. Two days before admission, intermittent, cramping, low abdominal pain began and was accompanied by a moderate yellowish vaginal discharge. The pains became progressively more severe until the day before admission when the patient removed the uterine packing. This was followed by the loss of a large amount of blood, which required 12 changes of perineal pads in 24 hours. At this time the patient developed fever and shaking chills, severe malaise, generalized myalgia, and nausea with repeated emesis, so that not even fluids were retained. On the day of admission she noted dark urine but no dysuria, frequency, or pain on urination. The urine output was believed to be small. Her temperature continued to rise and she was brought to the hospital in a delirious state.

Subsequent therapy. During the first 12 hours after admission the patient received 900 ml. of fluids, including 400 ml. of normal saline and 500 ml. of whole blood. The total measured fluid output was 500 ml., 250 ml. of which was emesis and 200 ml. loose, watery feces. Evaluation of fluid balance at this time suggested a fluid deficit of at least 5,000 ml. secondary to pernicious emesis, vaginal bleeding, and high fever. The patient had retained virtually no fluids in the 48 hours prior to admission. An acute water-loading test with 1,500 ml. of 2.5 per cent glucose in 0.45 per cent saline was given over a period of 2 hours without any appreciable urine output. The patient vomited 250 ml. of fluid within this time and an additional 1,500 ml. of glucose in 0.45 per cent saline was given in the succeeding 12 hours. A further drop in hemoglobin to 5.2 Gm. per 100 ml. necessitated a second transfusion of 500 ml. of whole blood. Vaginal bleeding had become scant in amount and Pitocin was discontinued.

Aqueous penicillin, gas gangrene, and tetanus antitoxins were discontinued after 48 hours, and the patient was maintained on 1.2 million units of procaine penicillin daily. Amphojel, 20 ml. orally four times a day, was begun and testosterone propionate, 25 mg. subcutaneously was given daily. The patient was fed salt-free buttersugar candy by mouth which forced feeding to tolerance. It was taken well at first, but more and more difficulty was met in forcing the candy, although at all times caloric intake exceeded 600 calories per day. Hemolysis continued and necessitated two further transfusions of blood. The patient continued to have a low grade fever of 99 to 101 degrees, explained, in part, by a heavy growth of Aerobacter aerogenes in cultures of the urine. This was attacked with 100 mg. Furadantin every 12 hours, beginning at the time that urine output increased.

The patient remained severely oliguric for 14 days. Apart from moderate irritability, occasional nausea, complaints of back and muscle aches, and occasional lower abdominal discomfort, she felt relatively well throughout most of the oliguric period. The serum electrolytes remained in surprisingly good balance except for moderate acidosis, steadily rising levels of blood nonprotein nitrogen, creatinine, and serum phosphorus. Although the serum potassium never rose above 4.3 mEq. per liter throughout the oliguric phase, ECG evidence of hyperpotassemia never developed.

Diuresis began on the fourteenth day after admission to the hospital and it was not until the seventeenth day that the urine output reached 2,000 ml. in 24 hours. During the diuretic phase, fluids were given freely and supplemental electrolytes were given by mouth according to renal loss measurements. At no time was there potassium diuresis; sodium and chloride loss was moderate. With diuresis the blood nonprotein nitrogen, creatinine, and serum phosphorus fell slowly, so that 3 weeks after the onset of diuresis these substances were present in normal amounts. The patient made a complete recovery and was discharged on the thirtyeighth day after admission. She has since become pregnant again and is doing well.

Comment

Once infection with virulent Cl. welchii is established, a fulminating illness is apt to occur. The patient has the onset of fever, often with shaking chills, prostration, anorexia, nausea, and vomiting. Diarrhea may be present but is seldom a cardinal sign. Uterine and general abdominal pain may be very severe, particularly in the presence of physometra or uterine emphysema. Severe generalized muscle pain may be a most striking complaint and is usually due to the alpha-toxin of Cl. welchii.1 Metastatic gangrene of muscle may rarely be a cause of muscle pain in these cases. Jaundice may be found with or without hemolysis,2 hepatic insufficiency apparently ensuing in the latter cases. Shock, pulmonary edema, and death may occur rapidly and are related to sepsis, hemolytic anemia, methemoglobinemia, and the ill-defined effects of Clostridial exotoxins. Marked leukocytosis is the rule, and spherocytosis in the peripheral blood smear has been stressed³ as a concomitant of Clostridial sepsis.

Although the general symptomatology presented here can be closely mimicked by the ingestion of excessive quantities of quinine, turpentine, or other poison, the treatment of these poisonings is purely supportive. The keynote of successful treatment in septic abortion with *Cl. welchii* infection is, we feel, the early recognition of the disease and the institution of specific therapy.

When Cl. welchii infection is suspected, it would appear advantageous to empty the uterus as soon as possible since it has been shown that, in gas gangrene generally, the survival rate is greatly dependent upon the early débridement of necrotic tissue.4 The efficacy of gas-gangrene antitoxin has been questioned, although favorable reports for its early use have been published.1,5 Most reports on the value of gas-gangrene antitoxin have, however, been based upon its use or exclusion in conditions where complete wound débridement is assured. In uterine gangrene, complete débridement may not be possible so that Clostridial toxins continue to be released. With this rationale, therefore, gas-gangrene antitoxin was given to the patient presented here.

Survival rate during the first few days of renal shutdown has improved because of the vigorous management of sepsis, shock, severe anemia, and dehydration. It was not until reasonable fluid replacement therapy became the rule, however, that substantial improvement in subsequent prognosis occurred. Since 1945 several authors⁶⁻⁸ have stressed the necessity of giving a volume of fluids equal in amount only to that lost through skin, gastrointestinal tract, lungs, and urine. Indeed, Bull⁹ states, "We have not seen a patient with anuric uraemia dying in under fourteen days who has not shown in life signs of water overload and at necropsy evidence of gross pulmonary or cerebral oedema."

Summary

The case of a patient who survived *Clostridium welchii* septicemia with hemolysis, anuria, and severe constitutional illness is presented to illustrate modern management of the disease.

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Hydatidiform mole in relation to malignant disease of the trophoblast

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THE literature concerning hydatidiform mole and its sequelae is rich in all aspects. Descriptions of hydatidiform mole have been noted by writers as far back as Hippocrates.

More recently, the relationship between hydatidiform mole and chorionic malignant changes has been presented. The prior writings in regard to hydatidiform mole have thoroughly described the disease as to pathology, clinical details, and complications. Attempts have been made to correlate the histopathology with the incidence of malignancy. Hertig and Sheldon^{5, 7} carefully graded moles in relationship to trophoblastic activity. Hunt, Dockerty, and Randall¹⁰ also made a contribution in the same direction. Novak14, 15 made monumental contributions to the knowledge of trophoblastic disease; Acosta-Sison,1 Novak and Seah,15 Delfs,4 Hobson⁹ and others added to the extensive accumulation of facts and cases of hydatidiform mole and chorionepithelioma. The establishment of the Mathieu13 registry has been and will be a great advance in the study and understanding of this disease. Recently, Smalbraak¹⁶ noted many of the original contributions to the subject of hydatidiform mole.

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The demonstration of an effective chemotherapeutic agent within the past few years has made it necessary to re-evaluate our understanding of this disease. It is with this in mind that we have reviewed the material at our hospital.

Material

The material presented in this paper consists of all hydatidiform moles seen at the Jewish Hospital of Brooklyn from January, 1937, to Dec. 31, 1958. All patients were followed either to a subsequent pregnancy or for several years after the evacuation of the mole. In this time, 68 cases of hydatidiform mole were diagnosed. On review of all the available pathologic material, 5 cases were excluded from the group and reclassified as hydatidiform changes. This left 63 cases of hydatidiform mole, an approximate incidence of 1:1,800.

Pathologic analysis of the molar material

Differentiation between hydatidiform moles of low-grade trophoblastic activity and "hydatidiform changes," as frequently seen in placental tissue derived from abortions, is not always easy. In the latter the villi are not usually enlarged to the same extent as in a true hydatidiform mole, trophoblastic proliferation is minimal, and few of the villous cores are completely liquefied. As stated above, 5 of the cases origi-

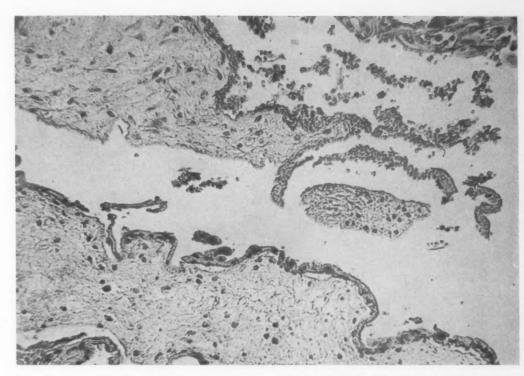


Fig. 1. Case 44. Photomicrograph showing a Grade I Mole. Note the relatively little trophoblast attached to the enlarged cystic and avascular villi.



Fig. 2. Case 63. Photomicrograph showing a Grade II mole. Note moderate amount of trophoblast and relative nuclear uniformity of both syncytial and cytotrophoblastic elements.

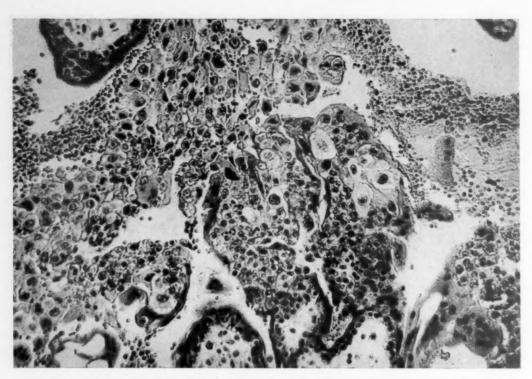


Fig. 3. Case 33. Photomicrograph demonstrating Grade III mole. Note the abundant trophoblastic elements and nuclear variability as to size and staining reaction.

nally classed as hydatidiform moles were reclassified as "hydatidiform changes."

Hertig and Sheldon,⁷ in their classic work, graded moles according to the anaplastic and trophoblastic activity of the tissue and demonstrated a relationship to the clinical outcome of the disease. Hertig and Mansell⁶ and also Hunt, Dockerty, and Randall,¹⁰ in other studies, have reduced the original 6 grades to 3. Any method of grading has shortcomings, but in our cases there was a high degree of correlation between the moles with anaplastic trophoblast and the subsequent development of chorioadenoma destruens and choriocarcinoma.

The histologic grading of the moles in our series was based entirely upon the qualitative and quantitative aspects of the trophoblast. Those classified as Grade I had relatively little trophoblast attached to the enlarged, cystic, and avascular villi (Fig. 1). Grade II hydatidiform moles contained a moderate amount of trophoblast and relative nuclear uniformity of both syncytial and cytotrophoblastic elements (Fig. 2). In

Grade III moles the trophoblastic elements were abundant and nuclear variability as to size and staining reaction was noticeable (Fig. 3). The final grade assigned to a mole was that of its seemingly most aggressive portions. Thus, not all molar villi of Grade III type contained exuberant, anaplastic trophoblast. This emphasizes the need for multiple blocks from the molar specimen. Twelve of the moles were graded as I, and in this group only one case became complicated. Eighteen of the cases were graded as II; in this group there were 2 complications. Twenty-nine moles were graded as active or III; in this group there were 7 complicated cases. In 4 instances we were unable to establish grade because of insufficient material; 2 became complicated. Coppleson³ and others have cast doubt on the practical value of grading moles. It is our belief, however, that the grading in combination with other factors suggestive of excessive trophoblastic activity as analyzed below increases the importance of the grade in determining the course of management

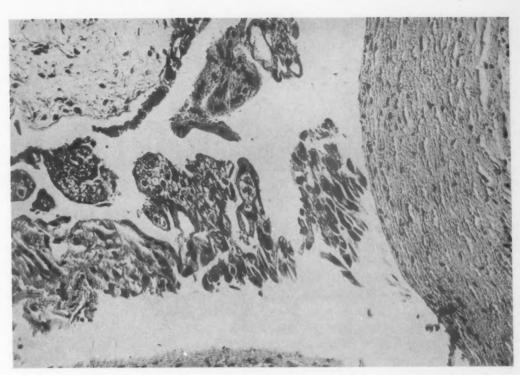


Fig. 4. Photomicrograph demonstrating invasive mole showing molar elements with villus within uterine muscle.

to be followed in a particular case. Table II lists the grades and subsequent malignancy.

Clinical pathologic analysis

The cases were classified in the following manner: uncomplicated moles, of which there were 51, chorioadenoma destruens, 8, syncytioma, 2, and choriocarcinoma, 2. (Table I). It is to be noted that throughout this presentation we have referred to our complicated cases as having shown malignant changes; this has been done for the ease of referral to this group and not necessarily because of any belief that such lesions as syncytioma or even chorioadenoma destruens can be classified so on the basis of examination of tissue.

The pathologic diagnoses of all but one of the complicated moles in this series were based upon hysterectomy specimens, and in one instance on a vaginal metastasis.

In this series the presence (Fig. 4) or absence (Fig. 5) of villi within the myometrium served as an excellent distinguishing feature between invasive mole and choriocarcinoma.

In the case of fatal choriocarcinoma complicating hydatidiform mole, 35 sections from the uterus failed to demonstrate the presence of chorionic villi and the patient died of pulmonary metastasis (Case 42).

The diagnosis of "syncytioma" unattended by evidence of invasive mole was made in 2 instances. The histologic features followed those described by Hertig and Sheldon.7 The uterine musculature in these instances contained groups of large cells with bizarre nuclei and glassy cytoplasm with surrounding areas of hemorrhage and inflammatory cells. The nature of the large cells is not readily apparent although the term used implies syncytiotrophoblastic origin. This is not the place to discuss the controversy between the use of the terms "syncytioma" and "syncytial endometritis" to indicate the condition so often found in postabortal or postgravid myometrium beneath the placental site. The lesion of "syncytial endometritis" is usually depicted

Table I. Incidence and classification of hydatidiform moles

	No.	%
Total hydatidiform moles	63	
Uncomplicated hydatidiform moles	51	80.9
Complicated hydatidiform moles	12	19.0
Chorioadenoma destruens	8	12.6
Syncytioma	2	3.1
Choriocarcinoma	2	3.1
Deaths	1	1.6

as large, isolated, deeply staining syncytiotrophoblast-like cells permeating the more superficial myometrium, especially in the neighborhood of blood vessels. The postmolar lesions illustrated by Hertig and Sheldon⁷ and present in several instances in this series consists of sheets of large cells with bizarre nuclei and an abundance of glassy cytoplasm (Fig. 6).

Gonadotrophic hormone determinations

Biologic tests by whatever method performed are of value in determining trophoblastic activity, retention of molar tissue, invasion by molar tissue, or the presence of distant metastases. Delfs established the value of quantitative chorionic gonadotrophin in the prognosis and treatment of hydatidiform mole and its complications. Her method depends on accurate assay of the blood serum; a basic knowledge of the levels of serum chorionic gonadotrophin in normal pregnancy is necessary to interpret these values. Most practicing clinicians do not have access to such an accurate test for chorionic gonadotrophin.

Follow-up on our patients included the Aschheim-Zondek test for gonadotrophins in the urine. Most of the cases of uncomplicated mole were negative for urinary gonadotrophic titers 4 weeks after expulsion of the mole (Fig. 7). The complicated moles showed a more persistent positive test and a higher titer. The gonadotrophic hormone tests on the urine prior to the emptying of the uterus were of significance. In 6 cases (one became complicated) there were negative results of the tests. Fifteen

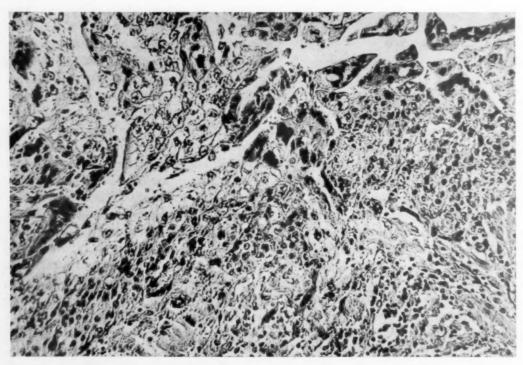


Fig. 5. Photomicrograph demonstrating choriocarcinoma in uterine musculature. Note the abundant trophoblast, nuclear variability, and absence of chorionic villi.



Fig. 6. Photomicrograph demonstrating syncytioma. Note sheets of large cells with bizarre nuclei in abundance of glassy cytoplasm.

cases showed positive results in undiluted urine; 9 of these were negative in dilutions and 6 had no tests done on diluted urine. Only one of these 21 cases was associated with malignant trophoblastic disease. Seventeen cases were positive in dilutions prior to evacuation of the uterus. Three were positive 1:100; one of these was malignant. One was positive 1:400; this case also was malignant. Two were positive 1:500; one of these was malignant. One patient had a titer of 1:600; the subsequent course was benign. Four cases showed urinary titers of 1:1,000; 2 of these subsequently became malignant. Four cases showed an initial titer of 1:2,000; one of these became malignant. The highest titer in our series was 1:4,000. In this group there were 2 cases; both became malignant. In 23 cases there was no recorded biologic test prior to evacuation of the uterus; one of these became malignant. One test was reported as doubtful, and one was unknown; both of these were malignant.

Significantly, in the complicated cases

with a known grade of the mole 6 of the 7 cases classified as Grade III showed positive tests in dilutions.

Coppleson³ stated that all his cases showing a titer of 1:200 or more after evacuation were proved to be invasive moles. However, it is known that a malignancy may exist with a lower titer or occasionally in the absence of a positive test, as one of our cases demonstrates (Case 20). Hobson⁹ showed that following evacuation of a mole the biologic test was negative in 28 days in most cases. In our own series all of the

Table II. Histologic grade with relation to incidence of complications in hydatidiform mole

	No.	Compli- cations	%
Total moles	63	12	19.0
Grade I	12	1	8.3
Grade II	18	2	11.1
Grade III	29	7	24.1
Unclassified	4	2	

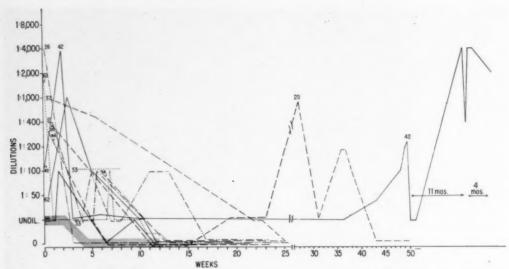


Fig. 7. Urinary gonadotrophin titers. Each of the separate lines represents the curve for each of the complicated cases. The heavy shaded curve is the composite curve for the uncomplicated moles.

benign cases had a negative biologic test in one month with the exception of 2, in which no tests were done for 3 months, at which time they were negative. Delfs4 reported 32 per cent of her cases as being positive 30 days after evacuation; again it should be pointed out that these determinations are serum levels and not urine tests. Studdiford and Decker¹⁷ believed that the pregnancy test is usually negative 8 to 10 days after complete evacuation of a hydatidiform mole. Fig. 7, a multiple line graph showing 12 separate curves each representing a complicated mole, demonstrates the persistence of urinary gonadotrophic hormones in these patients.

Clinical findings

The symptoms were not pathognomonic for mole. Bleeding was the most prominent symptom, being present in 62 of the 63 cases. The word "intermittent" was most frequently seen in the clinical descriptions of the bleeding. Severe nausea and vomiting were present in 13 of the patients and toxemia in 4; in addition one patient was hypertensive. Chesley, Cosgrove, and Preece² collected 35 cases of alleged eclampsia with mole. One of the patients in our

series (Case 17) was admitted with a diagnosis of fulminating toxemia. The uterus was emptied by means of abdominal hysterotomy; the diagnosis of mole was made on entering the uterus. In 20 of our cases pain was a noted symptom.

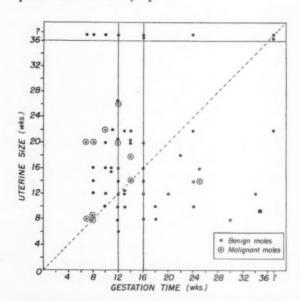


Fig. 8. Scattergram showing the relationship between uterine size and gestation time. Circled dots represent complicated cases. Note the increased relative size of the uterus prior to 12 weeks and the relatively decreased size after 16 weeks. Note the much greater frequency of oversized uterus in the complicated moles.

Age and parity

Age did not appear to be a very significant factor in this series. Investigation of parity did not reveal anything of significance.

Gestation time in relation to uterine size

Thirty-one patients were amenorrheic 12 weeks or less, 29 were amenorrheic more than 12 weeks, and in 3 the duration of amenorrhea was unknown. Examination of a scattergram (Fig. 8) relating gestational age to uterine size in weeks indicates that up to 12 weeks gestational age the uterus was larger than the gestation time. Between 12 and 16 weeks the uterus had become smaller than the gestational age, and, after 16 weeks, almost all the uteri were smaller in size than would be expected from the duration of amenorrhea. In plotting the malignant cases on the scattergram it was noted that 6 had definitely larger uteri than the gestation time, 2 were slightly larger, 2 were the size expected, one was smaller, and in one the size was unknown. These findings are interpreted as indicating the excessive trophoblastic activity in the complicated cases as demonstrated by the larger sized uterus in relation to the gestation time.

Diagnoses on admission

Table III lists the diagnoses on admission during early pregnancy. These were most often (60 per cent) referable to abortion, probably because of the appearance of bleeding.

Primary treatment

Table IV shows the type of initial evacuation and also the malignancy rate in reference to type of evacuation. Three patients had hysterectomies as the initial treatment. One of the hysterectomies was in an older woman in whom the mole was found in the laboratory as the hysterectomy was being performed for supposed leiomyomas. The other 2 hysterectomies which in the table are included in the hysterotomies

Table III. Admission diagnoses in hydatidiform mole

*	No.	%
Hydatidiform mole	17	26.9
Threatened abortion	7 1	
Incomplete abortion	14	
Missed abortion	8	
Imminent abortion	2 }	60.3
Inevitable abortion	3	
Complete abortion	2	
Abortion with fibroids	2	
Toxemia	1	
None	1	
Polyhydramnios	1	
Acute abdomen	1	
Fibroids with pregnancy	2	
Metastatic mole	1	
Dead fetus	1	
Total	63	

Table IV. Method of initial evacuation of hydatidiform mole and its relation to subsequent complications

No.	%	Com- plica- tions	%
51	81	6	12
11	17	6	55
1	2	0	0.0
63	100.0	12	19.0
	51 11 1	51 81 11 17 1 2	No. % plications 51 81 6 11 17 6 1 2 0

Table V. Total treatment in hydatidiform

Spontaneous expulsion and curettage	8
Spontaneous expulsion only	3
Dilatation and curettage	33
Two or more curettages	3
Hysterotomy followed by subsequent	
hysterectomy	6
Hysterotomy alone	. 3
Vaginal hysterotomy after spontaneous	
expulsion	1
Hysterectomy following other methods	13
Excision vaginal lesion after hysterectomy	1
Hysterectomy only	3
Irradiation after hysterectomy	3
Methotrexate after other therapy	3

were for excessive bleeding at the time of hysterotomy. The hysterotomies seem to be related in our series to the more active moles. Of the 11 patients undergoing hys-

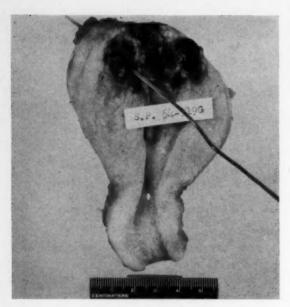


Fig. 9. Case 33. Photograph of cut uterus demonstrating invasive mole with perforation.

terotomies, 6 developed malignant trophoblastic disease; of these 6, 2 had choriocarcinoma; one, a syncytioma; and 3, invasive moles.

Total treatment

The multiple treatments to which our patients were subjected are listed in Table V. The spontaneously expelled moles were followed by a single dilatation and curettage in 8 patients. Thirty patients had a single dilatation and curettage. One patient had a vaginal hysterotomy following spontaneous expulsion of a mole.

There were 16 hysterectomies; all except the 3 described above were secondary to other treatment. Of the 16, 8 were for chorioadenoma destruens, 2 for choriocarcinoma, and one for syncytioma; the remaining 5 were for benign molar disease. Of the 5 hysterectomies for benign molar disease 3 were performed with no prior treatment as mentioned above. Another hysterectomy was done 2 weeks after curettage in a 42-year-old patient who continued to bleed and who had a uterus which remained subinvoluted. The fifth hysterectomy for uncomplicated mole was in a 35-year-old patient who spontaneously passed

a mole and then underwent curettage; the hysterectomy was done purely on the indication of the presence of a mole in a 35-year-old patient who had 4 living children.

Pitocin in continuous infusion was used in 5 cases; in 4 of these it proved to be of value in emptying the uterus as well as in controlling hemorrhage.

Radiation therapy was used in 3 patients. In one with choriocarcinoma (Case 20) it was used in full dosage to the pelvis; the patient is alive and free from disease 10 years after the initial evacuation. Radiation was also used in a patient with chorioadenoma destruens with pulmonary metastasis (Case 17). The pulmonary area and pelvis were irradiated, the lesions regressed, and the patient is alive and free from disease 11 years after hysterectomy. In another patient radiation was given to the pelvis following hysterectomy for perforating mole (Case 53); she is alive and free from disease 9 years after evacuation.



Fig. 10. Case 42. Photograph of cut uterus showing large area of necrotic hemorrhagic tissue wish choriocarcinoma.

Methotrexate was used in 3 cases; in 2, the drug was given late and in very inadequate doses by present standards. In the first it was given in the presence of advanced metastatic disease (Case 42). The second patient (Case 54) had vaginal metastases; here, too, the drug was administered in low dosage and only one course given. The third patient (Case 63) who had pulmonary metastases was given 3 full courses of Methotrexate as recommended by Hertz and associates8 and Li and co-workers.11, 12 The Aschheim-Zondek test became negative at the completion of the first course and the chest x-ray examination showed complete resolution of the pulmonary lesions at the end of 12 months.

Case reports

Case 17. E. K. was admitted to the hospital with severe toxemia. She had been amenorrheic 18 weeks; the uterus was the expected size. A hysterotomy was performed for toxemia and a Grade III mole was found and evacuated. One day later the urinary test for gonadotrophin was positive 1:400. Seven days after evacuation a chest opacity was found.

Three and one half weeks later curettage was performed because of the presence of a uterus the size of a 10 weeks' gestation, bleeding, and a positive undiluted urine test for gonadotrophin. One day later the test was positive 1:100. The chest x-ray examination confirmed the previous findings and a total hysterectomy and bilateral salpingo-oophorectomy were performed. The specimen showed chorioadenoma destruens.

Six weeks later the chest lesion showed some resolution. Deep x-ray treatment was given the right chest and pelvis. Nine months after evacuation of the mole the chest lesion was resolved. The patient is alive and well 11 years after the hysterotomy.

Case 20. D. L. was admitted with the history of 13 weeks of amenorrhea; the uterus was the size of a 24 weeks' gestation, and she complained of bleeding and vomiting.

A hysterotomy was performed and a Grade III mole evacuated. The urinary titer of gon-adotrophin was positive 1:400.

Urine tests for gonadotrophin were negative 4 and 5 months after evacuation. In the sixth month the test was reported as doubtfully posi-

tive and the patient bled slightly. One month later the urine test for gonadotrophin was positive and the uterus enlarged to 6 weeks size. Four weeks later, 8 months after evacuation, the test was positive 1:8,000. The following month a curettage was performed for missed abortion. The pathology findings showed endometritis. Ten months after the initial evacuation a total hysterectomy and bilateral salpingo-oophorectomy were performed. At this time the titer was positive 1:200. The pathology report was choriocarcinoma. The gonadotrophin test was negative one month after hysterectomy. Deep x-ray treatment was given to the pelvis.

The patient is alive and well 10 years later. Case 26. L. G. complained of bleeding and severe nausea and vomiting; she was 16 weeks amenorrheic and the uterus was the size of a 20 weeks' gestation.

The gonadotrophin test on the urine was positive in a dilution of 1:4,000. A hysterotomy was performed and a Grade III mole evacuated. The pathologist also reported syncytioma in the specimen.

The patient is alive and well 7 years after evacuation of the mole.

Case 33. L. R. was admitted to the hospital complaining of cramps, bleeding, and amenorrhea of 9 weeks' duration. The uterus was the size of an 8 weeks' pregnancy. The patient was discharged 3 days later with a diagnosis of threatened abortion. She was readmitted 2 days later with nausea, vomiting, and increased bleeding; curettage was performed the next day. The pathologist reported hydatidiform mole, Grade III. One month later curettage was repeated because of continued bleeding and a persistently positive Aschheim-Zondek test in undiluted urine. Gross molar tissue was obtained from the left cornual area. Four days later the urinary gonadotrophin was positive in a dilution of 1:100. One month after recurettage the patient was readmitted in shock with severe pain in the lower abdomen. Immediate laparotomy and total hysterectomy were performed; 2,500 c.c. of free blood was found in the peritoneal cavity and there was a fundal perforation (Fig. 9). X-ray films of chest and pelvis were negative. The postoperative course was uneventful. The patient is alive and well 5 years later.

Case 37. I. L. was admitted to the hospital with amenorrhea of 12 weeks' duration, cramps, and staining of 1 week's duration. The Aschheim-Zondek test was positive in dilution of 1:1,000

and the uterus was enlarged to 8 weeks size. She was discharged in 8 days with a diagnosis of threatened abortion and fibromyoma. Three weeks later she was readmitted; bleeding had continued and become profuse the day before admission; there was also nausea and vomiting. The uterus was now 3 fingerbreadths below the umbilicus. Mole was diagnosed and the uterus emptied with the use of Pitocin, sponge stick, and curette. The specimen was diagnosed as Grade III mole. One day later the urinary gonadotrophin titer was 1:500. Three months later the patient was readmitted; bleeding had occurred sporadically and for the last month had been more persistent. Urine had remained positive for gonadotrophin in the undiluted specimen. Four days later hysterectomy and bilateral salpingo-oophorectomy were performed. The pathologist reported invasive mole. One month later the Aschheim-Zondek tests were negative. The patient is alive and well 41/2 vears later.

Case 42. D. M. was admitted to the hospital after 14 weeks of amenorrhea; the uterus was the size of a 20 to 24 weeks' gestation. Her blood pressure was 146/90, and she had 2-plus albuminuria. The Aschheim-Zondek test was positive in dilution of 1:4,000. No fetal heart tones were heard and x-ray examination of the abdomen was negative for a fetal skeleton. An abdominal hysterotomy was performed and a mole evacuated. The pathologist reported a Grade III mole. The postoperative course was uneventful. Urinary gonadotrophins remained positive in undiluted specimens, and bleeding occurred at irregular intervals. Two months later, endometrial biopsy showed proliferative endometrium. The question of a new pregnancy arose 10 months after evacuation; with persistence of bleeding, curettage was done and proliferative endometrium obtained. Chest x-ray examination was negative; the urine was positive in 1:50 dilution. Bleeding continued, the urine became positive 1:200. Eleven months after evacuation of the mole, hysterectomy and bilateral salpingo-oophorectomy were carried out (Fig. 10). The pathologist reported uterus with choriocarcinoma. The chest x-ray findings were normal. Two weeks later urine was still positive but only in the undiluted specimen. Ten months later the patient had cough and hemoptysis. X-ray examination showed metastatic lesion in the left lower lobe with pleural effusion which on thoracentesis was positive for malignant cells. The Aschheim-Zondek test was positive in 1:5,000 dilution. Methotrexate was administered in 5 to 10 mg. daily doses. The patient died of the disease a little over 4 months later, about 26 months after evacuation of the mole. The postmortem examination showed choriocarcinoma of the left ureter, tumor thrombi in uterine veins, lungs with tumor thrombi, and kidney with hydronephrosis.

Case 44. N. D. was a grand multipara who spontaneously passed a mole. Urinary gonadotrophines were present in dilutions of 1:500. Hysterectomy was recommended but was refused. One month later she was readmitted with profuse bleeding and a positive Aschheim-Zondek test. Hysterectomy and bilateral salpingo-oophorectomy were performed. The specimen was reported as showing invasive mole and syncytioma. The chest x-ray examination was negative, and 8 days later the Aschheim-Zondek test was negative. The patient is alive and well 3 years later.

Case 53. H. B. was admitted with amenorrhea of 12 weeks' duration and the uterus enlarged to the size of a 24 weeks' gestation. On admission the patient complained of nausea and irregular bleeding for one month. The night prior to admission the patient bled profusely. A diagnosis of mole was made.

A hysterotomy was performed the day after admission and a Grade III mole evacuated. Gonadotrophin hormone was not detected in the urine one day postoperatively.

Eight weeks postoperatively the patient was readmitted in shock with a diagnosis of perforated uterus. A total hysterectomy and bilateral salpingo-oophorectomy were performed. The urinary gonadotrophins were positive in a 1:100 dilution. The extirpated specimen was reported as a uterus with chorioadenoma destruens.

Postoperatively the patient was treated with deep radiation to the pelvis. The patient is alive and free from disease 9 years after evacuation of the mole. This case was previously reported in the literature.

Case 54. D. S. was admitted to another hospital with an amenorrhea of 14 weeks. She spontaneously expelled a mole. Two days later a total hysterectomy was performed.

Six weeks postoperatively the patient was admitted to the Jewish Hospital bleeding vaginally. A large vascular lesion was removed from the anterior vaginal wall. The report was vaginal tissue with a molar villus and tropho-

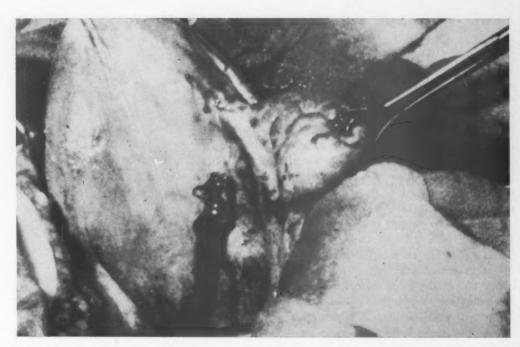


Fig. 11. Case 63. Photograph taken at operation demonstrating a perforating lesion in the right posterior surface of the uterus with free bleeding from the perforation.

blastic cells. The urine was positive for gonadotrophins in a 1:1,000 dilution; this became negative 6 weeks later.

Methotrexate in small doses was used. The patient is free of disease 2 years postoperatively.

Case 55. S. K. was admitted with a history of amenorrhea of 10 weeks' duration and bleeding. She was discharged with a diagnosis of threatened abortion. One month later she spontaneously expelled a hydatidiform mole. A curettage was performed. The urinary gonadotrophin test was positive 1:100.

One month later the patient was readmitted with staining. The uterus was the size of a 6 to 8 weeks' pregnancy. The chorionic gonadotrophin in the urine was positive in the undiluted specimen.

A dilatation and curettage, followed 5 days later by a hysterectomy and bilateral salpingo-oophorectomy, was performed. The specimen was reported as syncytioma.

A test for urinary gonadotrophin was negative 6 weeks later. The patient is alive and well 16 years later.

Case 62. A. L., a 43-year-old patient with amenorrhea of 16 weeks' duration and bleeding, spontaneously evacuated a mole after the administration of Pitocin. The urinary gonadotrophin test was positive at a dilution of 1:1,000.

One week later the patient was admitted for curettage. The specimen was a Grade II hydatidiform mole. The urinary gonadotrophin titer was positive in a dilution of 1:100.

Six weeks later the patient was readmitted and recuretted; the uterus was the size of a 6 weeks' gestation; the tissue was reported as hydatidiform mole. Four days later a total hysterectomy and bilateral salpingo-oophorectomy were performed.

The specimen contained invasive mole and syncytioma. Ten days after the operation the Aschheim-Zondek test was negative.

Case 63.* A. G., a 28-year-old para 2-0-0-2, was admitted on July 11, 1958; her last menstrual period had been on May 5, 1958. On June 4, 1958, the patient began staining intermittently in varying amounts; this continued until July 11, 1958, at which time the patient bled profusely. She was admitted to the hospital. At examination the uterus was noted to be the size of an 18 weeks' gestation; there was no fetal heartbeat present. The diagnosis on admission was hydatidiform mole. The cervix was long and closed. A chest plate was negative and the

^{*}This case is reported in detail because it represents the type of management we recommend.

flat plate of the abdomen showed a pelvic mass with no fetus present. The pregnancy test was positive at a dilution of 1:2,000 on July 13, 1958. The patient was given dilute Pitocin in a 1,000 c.c. infusion on 2 successive days with no change in the cervix. On July 17, 1958, an abdominal hysterotomy was performed and a hydatidiform mole evacuated. The tissue was reported by the pathologist to be a mole, Grade II. The pregnancy test was positive only in the undiluted specimen on July 21, 1958. The patient was discharged on July 24, 1958, after an uneventful course. She was well until Aug. 25, 1958, when she started to stain. On September 4, the uterus was found to be the size of a 6 weeks' gestation with moderate tenderness in the right parametrial area. The biologic pregnancy test on the urine done at weekly intervals had remained positive in the undiluted specimen and negative in the diluted specimen.

The patient was readmitted to the hospital on September 5, with the diagnosis of invasive mole and a possible perforation of the uterus. The urinary gonadotrophin test at this time was positive in a dilution of 1:100 and negative at 1:200. On Sept. 10, 1958 a dilatation and curettage was performed; the pathologic material was reported as decidual tissue and glands. Therefore, on September 12, a total hysterectomy was performed. At operation a small perforation (Fig. 11) in the posterolateral aspect of the uterus was found; this area was bleeding slowly. The specimen was reported as uterus with invasive mole. The biologic test was positive in the undiluted specimen postoperatively. The dilutions were negative. The patient recovered with no untoward event and was discharged on Sept. 21, 1958. A chest x-ray film taken at this admission was negative. On October 4, three weeks after hysterectomy and with the urine test positive, the patient was readmitted to the hospital for Methotrexate therapy. She was given 25 mg. a day for 5 days from Oct. 5, 1958, through Oct. 9, 1958. She developed severe stomatitis which started on October 10. A chest plate taken on October 7 was positive for metastases and showed a bilateral "coin" lesion. On October 16 a chest x-ray film showed the original bilateral lesions with a question of additional metastases on the right. (See Fig. 12 for October 31 x-ray.) The pregnancy test on October 15 was positive in the undiluted specimen. The patient was discharged on October 18.

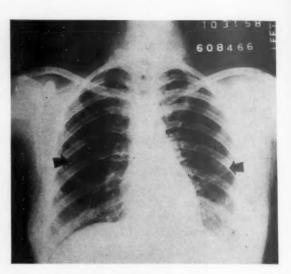


Fig. 12. Case 63. Chest x-ray showing bilateral pulmonary metastases. Six months later these lesions were no longer demonstrable.

The biologic pregnancy test became negative in all dilutions and in the undiluted specimen on Oct. 20, 1958, and remained negative thereafter. A second course of Methotrexate was started on October 28. The patient was again given 25 mg. of Methotrexate a day for 5 days. On November 1, she developed a rash on her neck; the following day the rash was on the neck and trunk, and stomatitis was present. On Nov. 3, 1958, the stomatitis was very severe with difficulty in swallowing. The chest x-ray film taken on Oct. 31, 1958, showed the same bilateral pulmonary lesions as previously described.

All liver function and kidney function tests were within normal limits. The toxic reaction to the Methotrexate was very severe. The patient developed extensive stomatitis, the white blood count dropped to 1,350 and the patient lost all her scalp hair, necessitating the wearing of a wig. On Nov. 12, 1958, the patient was discharged. A chest x-ray film taken on Dec. 5, 1958, showed resolution of the pulmonary lesion on the right side. Pelvic findings continued to be normal. A chest x-ray examination on Jan. 7, 1959, confirmed the clearing of the right side of the lung and also demonstrated beginning resolution of the pulmonary lesion on the left.

A longer interval of rest between courses was decided on because of the severe toxic reaction. On Feb. 16, 1959, the patient was readmitted to the hospital for another course of

Methotrexate; 125 mg. was given over a period of 5 days. The toxicity was much less severe. A chest x-ray film taken at this admission showed almost complete resolution of the chest lesions. X-ray examination on April 14, 1959, showed no metastatic lesions. Repeated x-ray films have shown no evidence of metastatic disease. The scalp hair has fully regrown.

Comment

From the material we have presented, it is our belief that hydatidiform mole is a tumor followed by serious chorionic disease in a high percentage of cases and should be treated actively. The malignant nature of this disease is sometimes slowly recognized. Three of the patients had perforations of the uterus while being observed clinically (Cases 33, 53, and 63). Two of the perforations led to severe hemorrhage and shock necessitating emergency therapy. Earlier determination of invasion or malignancy will lead to more prompt surgical and/or medical treatment.

We believe that there are four factors observable either before evacuation of the mole or immediately following the evacuation that can be helpful in determining the potential of invasion or malignancy. The height of the gonadotrophin levels in the blood or urine is one of these factors. The size of the uterus frequently is an indication of the degree of trophoblastic activity; the larger the uterus in relation to the period of gestation the more frequent will invasion or malignancy be present. The third factor is related to the ease with which the mole was evacuated. Simply stated, patients who are asymptomatic and in whom the first inkling of existence of mole occurs when there is complete spontaneous expulsion will very rarely have complications, whereas, conversely, the patient in whom symptoms persist with a strong suspicion of mole and in whom the uterus shows no tendency to empty itself will in a higher proportion of cases develop serious complications. Finally, the patient who shows evidence of marked trophoblastic activity in some portion of the molar tissue expressed has a much greater tendency to develop invasion or malignancy than those whose moles have minimal or no trophoblastic activity.

The other factor that is involved in determining the subsequent course of a mole is in the follow-up of the postexpulsion gonadotrophic titers. The presence of a positive test more than 2 weeks after expulsion is evidence of persistent chorionic activity. All our benign moles were negative not later than 4 weeks after expulsion.

As a result of these impressions a suggested course of action in association with moles is as follows: If there has been spontaneous expulsion of an unsuspected mole curettage should follow shortly thereafter. This is suggested even though there is some doubt as to the value of this procedure in the absence of heavy bleeding. If the diagnosis of mole is suspected and there is no evidence of spontaneous emptying of the uterus, the uterus should be surgically emptied at the point where there is no further suspicion of a normal pregnancy. This decision will be aided by the varying growth of the uterus, abdominal x-ray findings, and in some instances by the chorionic gonadotrophin titers in the urine or blood. If the uterus is small (up to 12 weeks in size) termination can usually be accomplished by dilatation and curettage. If the uterus is over 12 weeks in size it should be emptied by abdominal hysterotomy or by hysterotomy immediately followed by hysterectomy in those patients in whom further childbearing is no longer anticipated.

Postevacuation observation should be active and a definite plan must be followed. The molar tissue should be thoroughly examined in the pathology laboratory. Many blocks should be cut from various parts and examined for trophoblastic activity.

Biologic tests should be performed quantitatively every 2 weeks following expulsion of a mole. Most of the cases will have negative tests at the end of 4 weeks. If, however, the tests remain positive for 4 weeks with or without a rising titer, a dilatation and curettage should be done. Molar tis-

sue in the uterus at this time would suggest another waiting period of 4 weeks. If no molar tissue is found in the uterus at curettage at the end of 4 weeks and the biologic test is positive or shows a rising titer, hysterectomy should be done. The assumption is that chorionic tissue is present and, since it is not in the uterine cavity, it is most likely in the wall of the uterus or beyond. In the light of the suggestive value of Methotrexate a course of the drug may be tried at this point in an attempt to save the uterus in the very young woman with the disease or in a patient without a child. If this has been successful in producing a negative test for gonodotrophins, further courses of this drug should be given.

Following hysterectomy, quantitative biologic tests, serial chest x-ray examinations and repeated pelvic examinations should be done. The biologic tests should be performed at weekly intervals for 4 weeks and then each month for 12 months followed by every other month for another 12 months.

If the biologic test is positive 2 weeks after hysterectomy, there is a suggestion that local pelvic recurrence or metastatic disease elsewhere is present. It is our belief at this time that chemotherapy with Methotrexate should be started after the manner described by Hertz, Bergenstal, Lipsett, Price, and Hilbish. In the presence of proved metastases, chemotherapy would be started earlier.

With the advent of chemotherapy and its great possibilities in the treatment of this disease and also with the knowledge that the finding of a villus in an invasive lesion does not guarantee against a fatal result we believe that a more aggressive approach to this disease must be taken.

Summary

- 1. Sixty-three cases of hydatidiform mole, an incidence of 1:1,800, are reported.
- 2. Twelve cases (19 per cent) were complicated moles according to the classification used.
- 3. There were 8 cases of chorioadenoma destruens, 2 with pulmonary metastases.
- 4. Two cases of choriocarcinoma were in the group. One of these patients died of the disease, giving a mortality rate of 1.58 per cent for the entire series.
- 5. Two cases of syncytioma are included among the complicated moles purely by reason of the accepted classification.
- 6. The correlation between histologic grading of moles and the subsequent development of malignant trophoblastic disease is high.
- 7. The clinical features suggestive of malignant trophoblastic disease include the disproportionate large size of the uterus, the high level of the chorionic gonadotrophin excreted in the urine and the need for abdominal evacuation of the mole.
- 8. The importance of repeated chorionic gonadotrophin determinations in the management of complications of molar disease is stated.
 - 9. The use of Methotrexate is discussed.
- 10. Summaries of the 12 complicated cases are presented.

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Chorioadenoma destruens in a uterus duplex bicornis

Report of a case

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The literature on congenital uterine deformities contains only a few reports on the occurrence of neoplasms. While most tumors in deformed uteri may occur by chance, a review of the incidence of neoplasms in altered structures and environment is of interest. Because of the known high rate of abortions in the presence of deformed uteri and in view of their suggested pathogenesis, this applies particularly to chorionepitheliomas and chorioadenomas. The case reported herein is, to the best of our knowledge, the first recorded instance of a chorioadenoma destruens in a double uterus.

The patient was a 28-year-old housewife who was known to have a uterus bicornis and who was admitted on July 13, 1959, to the Hospital of the Good Samaritan for a hysterectomy because of habitual abortion. The patient's parents and one brother were living and well, but one of 2 sisters had had 9 abortions and one infant who died at term.

The patient herself was a gravida x, para iii, who had had 7 abortions and, over a period of 7 years, had had 2 full-term pregnancies delivered by cesarean section in 1953 and 1957; a cesarean section in 1956, at 8 months, which resulted in the delivery of a congenitally malformed infant who died at the age of 6 hours; and 7 early spontaneous abortions, 3 of which required uterine curettement. In 1953 the patient had a double

From the Departments of Pathology and Gynecology, Hospital of the Good Samaritan. pregnancy in the two compartments of the uterus. At the time of the abortion of these pregnancies, a vaginal septum was incised. The last abortion requiring curettement occurred in 1958. A second, later abortion in 1958, and the last one, in late May, 1959, apparently were complete. When not pregnant, the patient had regular menses, but she had had no menstruation since the last abortion in May, 1959.

The physical examination showed a redundant strip of mucosa, representing the remnants of the vaginal septum, to extend the full length of the vagina at 12 and 6 o'clock. There was a double cervix, and the uterus was bicornuate. Review of systems, complete physical examination, chest x-ray examination, complete blood count, and urinalysis were normal.

Because the patient had come to present a physiological as well as a psychological problem and because sterilization of the healthy husband was not considered advisable, an abdominal hysterectomy was performed on July 14, 1959. The uterus was found to be bicornuate, with a larger left horn. The tubes and ovaries were normal and were not removed. The operation, as well as the postoperative course of the patient, was uneventful, and she was discharged on July 18, 1959, 4 days after operation, in good condition.

The pathology report described the uterus as weighing 100 grams and as having a single, relatively small exocervix, with 2 patent, completely separated endocervical canals. There were 2 corpora; the larger left corpus and corresponding cervix measured 10.5 by 5 by 4 cm., whereas the smaller right one measured 8.5 by 3.5 by 3 cm. The septum separating the two endocervical

canals measured 4 mm. in thickness. The joined lower portion of the uterus measured 5.5 cm. in length. The endometrium was thin and pink-red. In the myometrium of the left fundus was a wellcircumscribed, firm, dark red, markedly hemorrhagic nodule measuring 3.2 by 3.2 by 3 cm. (Fig. 1). The microscopic examination of this nodule shows markedly hemorrhagic and necrotic tissue which contains numerous well-formed, slightly fibrosed, relatively avascular chorionic villi (Fig. 2). The villi are generally covered by a single layer of typical syncytial cells, and no atypical trophoblastic proliferation is noted. The necrotic portions of the lesion are infiltrated by many polymorphonuclear leukocytes. In certain areas the lesion is poorly demarcated from the surrounding myometrium, but there is no demonstrable vascular invasion.

Comment

Tumors in deformed uteri, excluding leiomyomas, are rare. Von Franque, in 1930, reviewed 23 cases of uterine carcinoma in coexistence with uterine anomalies. Nine of these cases were carcinomas of the fundus and 14 were cervical carcinomas.1 We were able to find reports on an additional 13 cases which were published since 1930.2-12 This number includes 6 carcinomas of the cervix. 6 carcinomas of the fundus, and one chorionepithelioma, 12 giving a total of 20 carcinomas of the cervix, 15 carcinomas of the fundus, and one chorionepithelioma. It is impossible to compare accurately the incidence of carcinomas in deformed uteri with that in normal uteri, because undoubtedly many cases have not been reported, and the true incidence of uterine anomalies is not known, the figures given in the literature varying from 1:500 to 1:2,000 women, 13, 14 approximately one third of these having bicornuate uteri. But if one estimates that one of approximately 1,000 uteri is congenitally malformed, 36 reported cases of cancer appear not excessive, and it can be assumed that uterine malformations do not significantly predispose to carcinoma. The fact that only one chorionepithelioma, and, in this paper, one chorioadenoma are reported is of interest because of the high rate of abortions in double uteri. Our case is a good example of this



Fig. 1. A large, well-circumscribed, hemorrhagic intramural nodule is seen in the left fundus after removal of the anterior half of the uterus.

phenomenon. The rate of abortions in double uteri is generally given as being from 21 to 53 per cent of all pregnancies. 18-17 It has been calculated that one of 15,386 abortions and one of 40 hydatidiform moles develop into chorionepitheliomas, and that one of 6 hydatidiform moles eventually becomes a chorioadenoma destruens. 18

Considering the above-stated incidence of uterine malformations and the associated high rate of abortions, it is a conservative estimate that well over 100,000 abortions and presumably a certain number of hydatidiform moles have occurred in deformed uteri during the last 50 years. The rare occurrence of chorionepitheliomas and chorioadenomas under these circumstances suggests that abortions or pregnancies in malformed uteri are not associated with a higher incidence of chorionepitheliomas than abortions or pregnancies in normal uteri. This is in contrast to the incidence of chorionepithelioma in ectopic pregnancies, which has been calculated as being 1 in 5,333.18 Further-

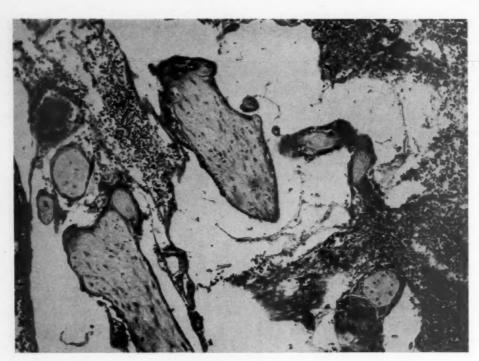


Fig. 2. High-power view of well-differentiated chorionic villi in myometrium.

more, the lack of an increase in the incidence of hydatidiform moles and chorioadenomas indicates that the pathogenic factor which is considered responsible for these conditions, namely, absence of or early death of the embryo,18 is not significantly more common in pregnancies in deformed uteri, and therefore is probably not the factor responsible for the high rate of abortions. Our own case may have been an exception. No pathology report on the abortion which preceded the discovery of the chorioadenoma by approximately 7 weeks is available, but it is certainly possible and, because of the generally accepted pathogenesis of chorioadenomas, probable that there were hydatidiform changes in the placental tissue. If these changes were caused by an early death of the embryo, it is interesting to note that the patient's second child, as mentioned above, was also congenitally malformed and died shortly after delivery.

Summary

A case of chorioadenoma destruens in one horn of a uterus duplex bicornis is reported. This apparently is the first recorded case of this type. The incidence of tumors and especially of chorionepitheliomas and of chorioadenomas in malformed uteri is briefly reviewed. The incidence of the latter lesions is found to be very low in view of the high rate of abortions in double uteri.

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Effect of alloxan-induced diabetes on the pregnancy of rats

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The fetal hazards accompanying pregnancy in the diabetic human have been recognized for many years¹⁻¹⁰ but the causes of excessively large fetuses, late intrauterine death, and increased neonatal mortality are still unknown. There is strong evidence that the causes of these adverse effects are present for many years before the development of manifest diabetes.^{4, 7, 11-15} When these effects occur in conjunction with an impaired glucose tolerance in the puerperium, such patients are considered to be prediabetic.¹⁶⁻¹⁷ There is, however, need for much more clinical and experimental investigation of these relations.

An experimental diabetic syndrome characterized by the acute necrosis of the pancreatic islets, hyperglycemia, and glucosuria can be produced in animals by the administration of alloxan. There are many conflicting reports of the effects of alloxan-induced diabetes on pregnancy but none have been found on the effects of an impaired carbohydrate metabolism, comparable to the prediabetic state in man, on pregnancy in animals. The present investigation was undertaken to clarify the effects of alloxan diabetes and "prediabetes" on pregnancy in rats.

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Method

Virgin female Sprague-Dawley rats weighing 200 to 250 grams, allowed chow and water ad libitum, were given alloxan (0.016 Gm. per 100 grams of body weight) subcutaneously.³² Daily weight, 24 hour urine volume, and urinary glucose level were determined during the next 3 or 4 days and in some animals the fasting blood sugar was measured, on samples obtained from the tail, by the micromethod of Nelson³³ and Somogyi³⁴ as modified by Natelson³⁵ and King.³⁶ Some animals which were not overtly diabetic were subjected to an oral glucose tolerance test (1.5 Gm. per kilogram as a 10 per cent solution).

Persistent glucosuria, polyuria, polydipsia, weight loss, and hyperglycemia were the criteria for the diagnosis of diabetes mellitus in the experimental animal. When the fasting blood sugar was normal but the oral glucose tolerance curve showed impairment of carbohydrate metabolism, the animal was considered to be comparable to a prediabetic.

Seven to 10 days after administration of alloxan, the animals were placed with male rats. If sperm were found in the vaginal smear or a marked weight gain occurred, the females were considered to be pregnant and were placed in individual metabolism cages.

All litters were delivered spontaneously; the individual pups were weighed immediately. Some pups were decapitated, sectioned sagittally, and dried at 90° C. for 24 hours. Blood was obtained at decapitation for glucose determination.

Results

One hundred and forty-four virgin female rats received alloxan and 88 became diabetic. Eight animals were given alloxan again and 7 subsequently became diabetic. All of these animals developed severe glucosuria, but, as expected, ketonuria was not observed. All of a random sample of 17 of these animals had a significant fasting hyperglycemia (654.2 ± 39.86 mg.* per 100 ml.) when compared to 5 control rats (95.4 ± 5.94 mg. per 100 ml.) 48 hours after the administration of alloxan. Forty-seven of the diabetic rats (49.5 per cent) died within one week: these animals had a significant weight loss of 12 per cent. Treatment with protamine zinc insulin reduced the early weight loss and salvaged 8 severe diabetic

Some of the 49 animals that did not become diabetic after alloxan showed a mild transient glucosuria. A random sample of 9 of these animals had normal fasting blood sugar determinations (131.0 \pm 1.9 mg. per 100 ml.) when compared to 5 control animals (127.2 \pm 5.4 mg. per 100 ml.). All of another random sample of 11 of these animals showed consistently impaired oral glucose tolerance curves (Fig. 1). Accordingly, this group of 49 animals were designated "prediabetic."

Forty-eight diabetic and 49 prediabetic animals were placed with males of proved fertility and eventually 26 diabetic and 36 prediabetic animals were delivered of litters. Six of the diabetic animals were treated with protamine zinc insulin (2 to 7 I. U. per day) to maintain a glucose-free urine. The number and weights of the pups born to these animals are compared to those born to 45 control rats in Table I.

The control animals were delivered of 9.1 \pm 0.43 pups per litter with a mean pup weight of 6.09 \pm 0.039 grams (3.5 to 9.1

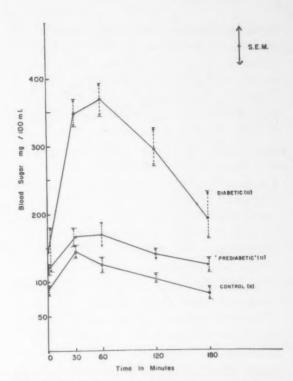


Fig 1. Oral glucose tolerance tests on pregnant alloxan-induced diabetic and prediabetic rats.

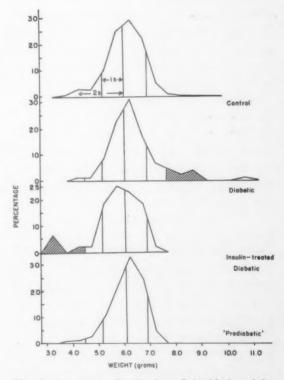


Fig. 2. Frequency distribution of the birth weights of pups born to alloxan-induced diabetic and prediabetic rats as compared to weights of those born to control animals.

^{*}Mean ± standard error of mean.

Table I. Litters of diabetic and control rats

							S	tillbirths
	No. of litters	No. of pups	Mean No. of pups per litter	Mean litter weight (grams)	Mean pup weight (grams)	Mean live pup weight (grams)	Rate*	Mean weight (grams)
Control (C)	45	408	9.1 ± 0.42†	55.28 ± 0.805	6.09 ± 0.039	6.07 ± 0.046	14.9	6.20 ± 0.010
Diabetic (D)	20	153	7.7 ± 0.67	48.88 ± 4.241	6.39 ± 0.077 C‡	6.18 ± 0.054	17.6	7.40 ± 0.282 C
Insulin- treated diabetic (ID)	6	47	7.8 ± 1.30	45.42 ± 8.781	5.80 ± 0.118 C D	5.85 ± 0.071 C D	36.5	5.72 ± 0.293 D
Prediabetic (PD)	36	326	9.1 ± 0.38	55.27 ± 2.553	6.10 ± 0.033 D ID	6.14 ± 0.041 ID	17.7	5.93 ± 0.024 C D

*Stillbirth rate = number of stillbirths per 100 births.

†Mean ± standard error of mean.

‡Significantly different from group indicated.

Table II. Comparison of diabetic and control litters in which mean pup weight exceeded 7 grams

No. of pups	No. stillborn	Fetal weight range*	Mean fetal weight ± standard error of mean (grams)
Diabetics			
9	0	6.522 - 8.342	7.19 ± 0.205
9	9	7.647 - 10.903	8.69 ± 0.229
4	2	7.002 - 8.220	7.59 ± 0.251
4	4	7.397 - 8.257	7.88 ± 0.180
3	2	6.663 - 8.640	7.42 ± 0.617
2	. 0	6.914 - 7.784	7.35 ± 0.434
31	17 (54.8%)		
Controls			
4	4	6.659 - 9.069	8.07 ± 0.521
2	2	6.138 - 8.031	7.08 ± 0.171
6	6 (100%)		

*Mean fetal weight of control litters, 6.09 ± 0.039 grams; incidence of stillbirths in control litters, 14.9 per cent.

Table III. Water content of fetal carcasses

	No. of pups	Initial weight (grams)	Dry weight (grams)	Per cent body water
Control (C)	126	6.05 ± 0.062*	0.83 ± 0.008	86.08 ± 0.139
Prediabetic (PD)	140	5.96 ± 0.051	0.83 ± 0.007	86.18 ± 0.061
Diabetic 16		6.75 ± 0.188 C0.001† PD0.001	0.93 ± 0.034 C0.01 PD0.01	86.21 ± 0.192

*Mean ± standard error of mean.

†P value for comparison with group designated.

grams) (Fig. 2). The untreated diabetic rats were delivered of fewer pups, but these were significantly heavier (6.39 ± 0.077 grams). Ten per cent of these pups weighed in excess of 7.5 grams in contrast to 2 per cent of the pups born to the control rats (Fig. 2). The stillborn pups were especially heavier (7.40 ± 0.282 grams) than their live litter mates. Table II compares the diabetic and control litters in which the mean pup weight exceeded 7 grams. The animals treated with insulin were delivered of fewer pups and these were significantly lighter than those of the controls. There was no significant difference between the number or weight of the pups born to the prediabetic and those born to the control animals.

The incidence of stillbirths was increased in the litters born to the untreated diabetic (17.6 per cent), the prediabetic (17.7 per cent), and the insulin-treated diabetic rats (36.5 per cent) compared to that in the controls (14.9 per cent). There was no difference in the length of gestation of the diabetic (11 animals), prediabetic (17), or control (15) animals as measured from the observation of sperm in the vaginal smear to delivery. Nor was there any significant difference in the water content of the carcasses of the pups born to diabetic, prediabetic, and control rats (Table III). The mean blood sugar level of the pups born to the diabetic rats (84.1 ± 7.57 mg. per 100 ml.) was significantly lower than that of the pups born to the control animals (130.7 ± 6.15); the mean blood sugar level of the pups born to the prediabetic rats (107.1 ± 16.54) fell between that of the diabetic and that of the control animals.

Comment

The effects of experimental diabetes mellitus on pregnancy have been investigated in pancreatectomized animals,29 when alloxan has been administered during pregnancy,22, 80, 81 and when alloxan diabetes has been induced before conception.22, 23, 25-27 The last condition appears to be most comparable to pregnancy in the diabetic woman. Davis and co-workers found that pregnancy was abnormal in 4 animals made diabetic before conception, with fetal death and absorption after the twelfth day of gestation, and they concluded that it was not feasible to investigate this problem in such animals. Although pre-existent diabetes is known to alter the estrus cycle and diminish fertility in the rat, 22, 25-27 successful pregnancy was observed in 26 diabetic rats in this experiment.

The observation of Miller²³ that litters born to diabetic rats are of normal size and weight is supported by others.25-27 In the present investigation, however, the diabetic rats were delivered of smaller and lighter litters. Nevertheless, the individual pup weight was significantly greater than in the controls. Particularly impressive was the greater weight of the stillborn fetuses. Other workers27, 29 have also noted the increased weight of the stillborn pups of diabetic rats. The stillbirth rate of 17.6 per cent is comparable to that found by Lindan and associates27 and Barns.87 Hoopes88 obtained large stillborn fetuses by prolonging the gestation of normal rats. Wells and co-workers30 have reported that gestation was prolonged by 25 hours in 8 rats given alloxan on the twelfth day of gestation but that the pups of these animals were of normal weight. Indeed, they found that the birth weight was reduced by 14 per cent when the pups were delivered by cesarean section 519 hours after observed mating, i.e., 25 hours before the estimated time of spontaneous delivery. Although we do not know the exact hour of conception or parturition in our animals, we did not observe any difference in the length of gestation of 43 animals for which the day of mating and the day of parturition were known. The observation that the 6 diabetic rats treated with protamine zinc insulin produced smaller and lighter litters and had an increased incidence of stillbirths is at variance with that of other investigators. 22,28 The difference may be due to the degree of treatment. In our experiments, the diabetic rats were treated until there was no glucosuria and then maintained on that dose of insulin until term. Ferret and co-workers28 stated that the diabetes was not completely controlled in their series and Davis and associates²² used 0.75 unit of protamine zinc insulin compared to the 2 to 7 units per day used in our series.

The effects of mildly impaired carbohydrate metabolism on pregnancy in the rat has, apparently, not been investigated. Dunn and McLetchie¹⁸ noted that the destruction of the pancreatic islets may be incomplete in rats after the administration of alloxan, and Lazarow³⁹ has demonstrated the existence of a subdiabetic state in such rats as indicated by a normal postprandial blood sugar level but an impaired glucose tolerance curve. This impairment of the glucose tolerance was progressive, and one third of these animals became diabetic within one year. Nevertheless, Davis and associates²² have observed that animals that recovered from their diabetic state early in pregnancy were delivered of normal litters, and according to Sinden and Longwell²⁵ transient hyperglycemia did not interfere with reproduction. Wells and co-workers30 found that the fetuses born to rats which did not become diabetic after the administration of alloxan were of reduced weight at 519 hours of gestation and of approximately normal weight when delivered spontaneously. We observed no difference between the length of gestation, the litter weight, or the mean weight of pups born to the prediabetic rats and those born to the control animals. There was, however, an increased incidence of stillbirths.

There was no significant difference in the water content of the pups born to diabetic, prediabetic, and control animals when dried to constant weight. These results are consistent with those reported by Solomon³¹ and indicate that the increased weight of the diabetic litters was not caused by the retention of water.

Fetal hyperglycemia is coincident with maternal hyperglycemia.⁴⁰ The presence of hypertrophy of the pancreatic islets in still-births^{41, 42} and of hypoglycemia in the living newborn^{43, 44} from diabetic women suggests that the mother's condition has produced

fetal hyperinsulinism. Insulin has been shown by Salter and Best⁴⁵ to act as a growth hormone in the hypophysectomized rat. On the other hand, diabetes mellitus can be produced by excessive growth hormone, and Young46 has suggested that excessive growth of the fetus may be caused by excessive maternal production of growth hormone. Our present results are compatible with the working hypothesis that maternal hyperglycemia with resultant fetal hyperinsulinism is likely the cause of the larger babies of the diabetic mothers. There is, as yet, no evidence that alloxan increases the output of growth hormone. A decision as to the role of growth hormone in the etiology of large babies from diabetic mothers must await a precise assay of this hormone in blood and the demonstration that this hormone crosses the placental

Conclusions

1. Rats that were made diabetic with alloxan before becoming pregnant were delivered of fewer pups and lighter litters with an increased incidence of stillbirths. The individual pups, especially the stillborn ones, were significantly heavier than the pups born to the control animals. This weight increase was due neither to prolonged gestation nor to the retention of water by the fetuses.

2. Treatment of the pregnant alloxan diabetic rat with sufficient protamine zinc insulin to maintain a glucose-free urine produced a significant reduction in the birth weight of the individual pup and a very marked increase in the stillbirth rate.

3. Prediabetes in rats as indicated by transitory glucosuria and normal fasting blood sugar but an impaired glucose tolerance after the administration of alloxan had no apparent effect on the first pregnancy or litter.

4. The evidence obtained is compatible with the hypothesis that uncontrolled maternal hyperglycemia with coincident fetal hyperglycemia results in fetal hyperinsulinism and that the increased growth of the fetus is caused by the anabolic effect of this excess insulin.

We wish to express thanks to Miss Blanche Box, Mrs. Vera Feleki, and especially to Miss Sylvia Barta for technical assistance, and to the Ames Company for the supply of Clinistix.

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Ligation of the inferior vena cava in early pregnancy

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THROMBOEMBOLISM rarely occurs in early pregnancy and its treatment presents special problems. The reports in the literature concerning the use of Dicumarol in the pregnant patient are in conflict. The bulk of animal experimentation supports the view that Dicumarol crosses the placental barrier and causes fatal hemorrhage in the fetus. Schofield1 and Roderick2, 3 fed spoiled sweet clover to pregnant cows and the calves died of hemorrhage within 28 hours of birth. Quick4 fed Dicumarol to a pregnant dog before parturition and of the litter of 7 pups, 4 died of hemorrhage and 3, treated with vitamin K, survived. Sachs and Labate⁵ reported on a 23-year-old gravida iii, para ii, who developed phlebothrombosis and pulmonary embolism at 31 weeks of pregnancy; she was treated with heparin for the first 48 hours and then with Dicumarol. Intrauterine death occurred on the fifty-third day of treatment. Total amount of Dicumarol used was 3,150 mg. Fetal postmortem examination revealed hemorrhage into the thymus, pericardial sac, and the pleural cavities. On the other hand, Ullery6 reported the cases of 2 patients, one treated with Dicumarol and one with heparin, and both pregnancies terminated successfully.

Collins and his associates⁷⁻¹² reported on the ligation of the inferior vena cava and both ovarian veins for suppurative pelvic thrombophlebitis. This operation was performed on 70 patients from 1942 to 1950. These patients were closely followed to determine the effect of the operation on peripheral edema, pelvic circulation, venous pressure, menstruation, and ovulation. In the course of the follow-up, 15 pregnancies were found in 11 patients. Six abortions occurred in 5 patients (one admittedly induced) and in the other 6 patients, 9 pregnancies were delivered at term.

Other successful pregnancies following ligation of the inferior vena cava only were reported by Burke and Rosenfield¹³ and Heath and Carpenter.¹⁴

A search of the American literature reveals only one case report of ligation of the inferior vena cava in early pregnancy. This case was cited by Young and Derbyshire. The patient, a 21-year-old primigravida, developed left iliofemoral thrombophlebitis on the twelfth postoperative day following an uneventful appendectomy during the tenth week of pregnancy. Ligation of the vena cava with regional sympathetic block was promptly done. The immediate postoperative course and subsequent pregnancy were uneventful. Spontaneous labor occurred at 39 weeks and a normal infant was delivered after 8 hours of labor.

It is because of the rarity of inferior vena cava ligation in early pregnancy and subsequent successful termination that the following case history is presented.

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Case history

The patient was a 28-year-old housewife, para 3-2-0-2, whose last menstrual period had occurred on June 8, 1956. The first pregnancy terminated in the pelvic delivery of binovular twins at 33 weeks after an uneventful prenatal course. The first twin, a 1 pound, 14 ounce anatomically normal male, died in 36 hours. The second twin, a 4 pound, 11 ounce male, had multiple congenital anomalies and died in 24 hours. The second and third pregnancies terminated in full-term normal deliveries and both children are living and well. The fourth pregnancy ended in the spontaneous delivery of a 4 pound, 12 ounce stillborn female at 40 weeks. Occult prolapse of the cord, a true knot in the cord, and a small, severely infarcted placenta accounted for this intrauterine death.

The past history revealed pleurisy at the age of 15 and a "mild" attack of poliomyelitis at 16. The family history was noncontributory.

On Aug. 28, 1956, the patient experienced a "grippe-like feeling" with fever to 101° F., abdominal cramps, muscular aches and pains, and one loose bowel movement. Three days later pain occurred in the right lower anterior quadrant of the chest radiating to the right shoulder and accentuated by deep breathing. Almost simultaneously with the chest pain, she noted pain in the left groin. All symptoms abated temporarily, and on September 3 pain recurred in the left groin and thigh and the left calf also became painful. The patient made her symptoms known on September 5 and was immediately admitted to the hospital.

The pertinent physical findings on admission were: temperature 101° F.; pulse 90; respirations 24; percussion and auscultation of lungs normal. There was tenderness in the left calf, the left thigh over Hunter's canal, and just above the medial portion of the left Poupart's ligament. The left thigh, measured 5 inches above the patella, was 11/2 inches greater in circumference than the right measured at the same level; the left calf, measured 5 inches below the patella, was 11/4 inches greater in circumference than the right measured at the same level; the entire left leg from groin to toes was cold and mottled. The following laboratory findings were recorded: hemoglobin level, 11.2 Gm.; hematocrit determination, 36; red blood count, 3.62 million; white blood count, 13,800 with a normal differential; x-ray of the lungs revealed no evidence of pulmonary infarct.

It was decided to treat this patient with anticoagulant therapy. Aqueous heparin was given every 4 hours through an indwelling catheter in the left cubital vein. The amount given was determined by the clotting time and varied between 35 and 50 mg. The clotting time was maintained between 16 and 22 minutes as determined by the Lee-White method. The daily dose of heparin ranged from 190 mg. to 360 mg. In addition, 600,000 units of procaine penicillin was administered intramuscularly each day. The left leg was elevated on a pillow and protected by a cradle. Pain was controlled with meperidine, codeine, secobarbital, and aspirin. By the sixth hospital day the measurements of the left leg became equal to those of the right leg, temperature and pulse became normal, and all pain disappeared. Beginning on the eleventh hospital day the dose of heparin was gradually reduced and finally omitted on the fourteenth day. At this point the patient was allowed out of bed with elastic bandages applied to both legs. No vaginal staining occurred during heparin therapy.

On Sept. 18, 1956, the thirteenth hospital day, the patient complained of a sore throat that persisted on the following day and in addition she noticed aching of the right side of the face and neck. Physical examination was negative and temperature, pulse, and respirations were normal. On Sept. 20, she was noted to be tense and anxious; the temperature was elevated to 100° F., pulse to 95, and respiration to 24 to 28 a minute. At this time she complained of sharp pain in the right lower part of the chest that was aggravated by deep breathing and a cough that produced bloody sputum. Auscultation revealed diminished breath sounds and friction rub in the right lower side of the chest posteriorly. In spite of the fact that x-ray examination did not confirm the diagnosis of pulmonary infarct, it was decided that surgical intervention was indicated.

On September 21, under general anesthesia, the vena cava was ligated just above the bifurcation. The immediate postoperative condition was excellent. No anticoagulant therapy was given. Pain in the right side of the chest gradually disappeared over the next 5 days. Moderate vaginal staining occurred on the third postoperative day and diethylstilbestrol following the Smith¹⁶ regime was instituted. The patient made an uneventful recovery and was discharged on the eighth postoperative day wearing full-length elastic hose.

Subsequently, the prenatal course was uneventful. Occasionally, there was mild aching of the right leg but there was never any demonstrable edema. Spontaneous labor began on Feb. 25, 1957, and after 9 hours and 30 minutes of labor, a normal, active 6 pound, 14 ounce female infant was delivered by low forceps. The postpartum course was afebrile and uneventful.

Postpartum examination on April 18 and Aug. 15, 1957, revealed no edema or varicosities of the lower extremities and they were equal in size. The uterus was anterior, symmetrical, normal in size, and freely movable. The vaults and sides were normal and the cervix well epithelized. Menstruation was re-established in June, 1957, occurring with the usual regularity every 25 days, but the duration of the flow was 7 days instead of the usual 4 to 5 days. There was no excessive bleeding, increased premenstrual tension, or dysmenorrhea. The patient was free from symptoms and ran her household with her usual vigor and vitality.

The patient has been checked yearly, the last visit being in April, 1959. She stated that she felt perfectly well, the menstrual cycle had not changed, and her legs had caused her no discomfort. The infant's mental and physical growth has been normal.

Comment

It was decided that heparin was the anticoagulant of choice in the treatment of the

acute thrombophlebitis since, from the available evidence it was thought that Dicumarol probably crosses the placental barrier. After 2 weeks of therapy all evidence indicated that the patient was cured. However, with the clinical evidence of pulmonary embolism so shortly after heparin therapy was omitted, it was decided that ligation of the inferior vena cava would probably be the safest course to follow. The vaginal staining that occurred on the third postoperative day probably was a manifestation of the temporary congestion of the uterine circulation until the collateral circulation was completely taken over by the portal, vertebral, and azygous systems.

Summary

The literature on ligation of the inferior vena cava in early pregnancy and in women during their childbearing era has been reviewed. As far as can be determined, the case presented here is the second case of ligation of the inferior vena cava in early pregnancy with a successful outcome.

The advice and help of Dr. Leon Ryack of the medical staff and Dr. John Sears of the surgical staff is gratefully acknowledged.

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Treatment of biliary stasis in the latter half of pregnancy

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EVERY obstetrician notices, in the latter half of pregnancy,¹ the high incidence of the disturbing symptom-complex known as biliary stasis. Although references are made to it in standard textbooks,^{1, 2} there is actually very little written on the subject. A thorough search of recent literature reveals hardly any activity in this field, although the syndrome is one of the most disabling encountered in routine obstetrical practice.

Objective evidence of gall bladder dysfunction is difficult to obtain in this disease, since most cases are not advanced enough to produce definitive physical or laboratory signs. Roentgenograms are contraindicated in pregnancy except in the most urgent cases, but in former days, when x-rays were taken more freely, pressure defects and nonvisualization were demonstrable.3 Symptoms therefore became the most reliable diagnostic criteria, and the following are considered to be the most characteristic: fat intolerance, constipation, nausea (to be distinguished from hyperemesis gravidarum), abdominal distention, gaseous eructation, indigestion, and pain in the area of the gall bladder.

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Many conditions are prevalent during pregnancy which could predispose to biliary stasis with subsequent cholelithiasis and cholecystitis:

1. The encroachment of the enlarging uterus, with resultant displacement of the

gall bladder upward and to the right,³ predisposing to decreased gall bladder evacuation and stasis.

- 2. Increased intra-abdominal pressure,³ with the possibility of a further decrease in gall bladder evacuation.
- 3. The physiological hypercholesterolemia observed in pregnancy, leading to the deposition of cholesterol foci and subsequent cholelithiasis.
- 4. Passive hyperemia of the liver,² with possible cholangitis.
- 5. Increased rate of hemolysis,² leading to bilirubin calculi.
- 6. The increased incidence of infection, such as ureteritis,² with possible hematogenous spread to the biliary tract.

At the present time the only treatment generally employed is the limitation of fats and foods rich in cholesterol. Since biliary stasis can lead to chronic cholecystitis, cholelithiasis, and hepatic disorders,3 it is imperative, especially during pregnancy, for the gall bladder to be evacuated regularly.6 D-Glucitol,* C₆H₁₄O₆, has been found to be a potent cholagogic agent, the maximum contraction occurring after 30 minutes.6, 7 Concomitantly, the antispasmodic action of homatropine methylbromide also relaxes the sphincter of Oddi and dilates the bile ducts. By this reciprocal, combined action, fat digestion is aided and there is enhancement of absorption of fat-soluble vitamins A, D, E,

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^{*}p.-Glucitol, in combination with homatropine methylbromide, was supplied as ProBilagol by The Purdue Frederick Company, New York, New York.

and K. The properties and actions of this combination of drugs and the impressive results achieved elsewhere in the treatment of biliary-digestive malfunctions⁸⁻¹⁰ warranted a trial of it in the biliary stasis of pregnancy.

Material and methods

All patients in this study were in the latter half of pregnancy. Those who were chosen for therapy had sufficient symptoms of biliary dysfunction to warrant repeated complaints and frequent examinations. Thirty patients were placed initially on 5 ml. three times a day, before meals, of the solution containing 4.5 Gm. p-glucitol and 1 mg. homatropine methylbromide per each 5 ml. (teaspoonful). A control group of 26 patients received the same amount of a placebo identical in taste and appearance to the active drug.

After 2 weeks of treatment with the p-glucitol-homatropine solution each patient was questioned closely regarding her symptoms and the results were charted as follows: worse (-), no improvement (0), moderate improvement (+), marked improvement (++). Those patients showing no or only moderate improvement were then placed on a dosage of 10 ml. three times a day, before meals.

Patients who did not respond to treatment with the placebo after 2 weeks were given one teaspoonful of the active drug three times a day for a period of two additional weeks.

The criteria for response to treatment

were necessarily subjective since the alkaline phosphatase, serum bilirubin, and cholesterol levels were found to be elevated in only one case.

Results

The results of the study are summarized in Table I.

Of the 30 patients treated with the drug, 27 (90 per cent) exhibited marked or moderate improvement of symptoms and 3 (10 per cent) no improvement; none were made worse. Seven of the 10 patients who reported only moderate or no improvement were re-treated with double the original dosage (10 ml. three times a day); all of these patients reported marked improvement on the increased dosage.

Of the 26 controls treated with placebo, 7 (27 per cent) reported marked improvement of symptoms, none reported moderate improvement, and 19 (73 per cent) reported no improvement; again none were made worse. All of the 19 patients who reported no improvement on the placebo were then re-treated with 5 ml. three times a day of the p-glucitol-homatropine solution; of these, 17 (or 89 per cent) reported marked improvement, none reported moderate improvement, and 2 (11 per cent) reported no improvement.

Thus, of the total of 49 patients treated with the drug in the initial dose of 5 ml. three times a day, 44 (90 per cent) exhibited a significant degree of clinical improvement. The only untoward effect noted was laxation in one patient.

Table I. Results of treatment with drug and placebo

					Results			
Treatment (No. of patients in parenthesis)		Marked improvement			Moderate improvement		No improvement	
ProBilagol (30)	Original series (30) Re-treatment with in-	20	(67%)	7	7 (23%)	3	(10%)	0
	creased dose (7)	7	(100%)	0		0		0
Placebo (26)	Original series (26) Failures re-treated with	7	(27%)	0		19	(73%)	0
	ProBilagol (19)	17	(89%)	0		2	(11%)	0

Comment

The well-known fact that the first attack of biliary colic in women commonly occurs in the postpartum period² indicates that the biliary stasis of pregnancy may be more than just a troublesome symptom-complex requiring only symptomatic relief; it may also be a problem in preventive medicine. It is therefore possible that a therapeutic agent which corrects this biliary stasis may also prevent future cholelithiasis. On the basis of our consistently good results with an agent of this type in our small series of cases of biliary stasis in pregnancy, we feel that it merits considerably more use. Moreover, as

was noted above, if the recommended initial dosage fails to provide satisfactory improvement, the dosage should be increased until desirable results are obtained or until undesirable side effects are noted.

Summary

A solution of p-glucitol and homatropine methylbromide has been found to provide effective relief in a controlled series of cases of biliary stasis in the latter half of pregnancy. The results observed to date indicate that this cholagogue offers great promise in the treatment of a common and distressing complication of pregnancy.

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A double-blind laxative study on postpartum patients

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The restoration of "proper" bowel function in the puerperium is often a matter of concern to the patient, a concern not infrequently communicated to the physician. Actually, the motility of the intestinal tract diminishes during pregnancy, and normal delivery is often followed by a mild passing episode of ileus. In addition, the patient has frequently had a cleansing enema and has missed 1 to 4 meals during labor. Finally, the puerperal diuresis may well make less fluid available to the intestinal tract.²

These various factors not infrequently combine to make the re-establishment of bowel regularity somewhat delayed; a delay which becomes a leading topic of conversation and results in the administration of a large variety of medications designed to stimulate activity in the large intestine. Presumably, the prescribing of such medications by the obstetrician is motivated by a desire to circumvent the use of an enema, either because the enema is considered uncomfortable by the patient or nonphysiologic by the physician. The medical literature abounds in reports on these medications, but few if any studies have been carried out by the "double-blind" techniques.1, 3-5

The present report is concerned with the results of such a "double-blind" study of a medication which had been greeted with enthusiasm by the nursing staff and patients on

preliminary trial. It is designed to correct the condition of clinical sluggishness of the bowel by incorporating an active ingredient, specifically known to stimulate Auerbach's plexus, with a stool softener. Yasuna and Halpern⁶ determined by surface tension lowering curves that the optimal median dose of the stool softening agent dioctyl sodium sulfosuccinate was 50 mg. They also indicated that larger amounts of this surface-acting agent do not further decrease the surface tension. The length of time needed for stool softening is approximately 6 to 8 hours and for this reason an active peristaltic stimulant should not act sooner. Cassia acutifolia (senna) pods were used as the optimal peristaltic stimulant medication, to be used in combination with dioctyl sodium sulfosuccinate since its time of action is 8 to 10 hours after ingestion.7 The capsule used in this study contained 50 mg. of dioctyl sodium succinate and the standardized senna concentrate of active principles of 225 mg. of Cassia acutifolia pods. The recommended dosage was 1 to 2 capsules per day. This preparation in capsule form was convenient for the postpartum patient as well as for the nursing staff. Its action is confined to the colon and it is not transported in the breast milk.6

Method of study

All patients received the double-blind capsule beginning as soon post partum as was practical. Patients either received the laxative capsule or the placebo that contained inert ingredients. The dosage schedule was one capsule twice a day. The patient was intentionally not told the capsule was a laxative

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preparation and no other additional laxative medication was used. Enemas were not part of the "routine postpartum orders" and were given only if requested by the patient. The key to the double-blind study was not known until after the study was completed.

Randomly selected postpartum patients were also given the double-blind medication and along with the first capsule a swallow of barium was given. Serial x-ray films were obtained on these patients at 1 hour, 4 hours, 24 hours, 28 hours, and 32 hours and progress of the head of barium was noted. Eleven patients who received the laxative medication were studied in this manner and 9 who received the placebo were studied.

Results

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A total of 121 patients received the placebo medication and a total of 123 patients received the laxative medication. The average number of capsules needed in the placebo group was 4.32 before the first spontaneous bowel movement (2.55 days after delivery) as contrasted with the laxative group of 4.72 capsules before the first bowel movement (2.48 days). Thirty-one patients (25.6 per cent) in the placebo group requested a postpartum enema as contrasted to 20 (16.2 per cent) in the laxative group (Table I).

The parity of the patient altered the need for a postpartum enema to some degree and probably accounts for the minor divergence in the results of the number of enemas given. Fifteen primiparous patients were in the placebo group and 40 per cent of these patients requested enemas. Forty-four per cent of the primiparous patients in the laxative group requested enemas (Table II).

Fifty-four patients (45 per cent) in each study group nursed their babies, and no adverse effect was noted in any newborn infant that could be attributed to either the laxative medication or the placebo. Lactating mothers had a higher incidence of postpartum enemas than did the over-all group or the nonlactating mothers (Table III). The reason for this is not obvious but it may be the relative degree of dehydration associated with nursing. The increased excretion of

Table I

	Placebo	Senokap
Average No. pregnancies	4.72	5.96
Average No. deliveries	3.42	4.40
No. capsules before first bowel movement	4.32	4.72
No. days before first bowel movement	2.55	2.48
Postpartum enemas	31	20
Total No. patients studied	121	123

Table II

	S	enokap	Placebo			
	No. pa- tients	Enema	No. pa- tients	Enema		
Primiparas 9		4 (44%)	15	6 (40%)		
paras	114	16 (14.1%)	106	25 (23.6%)		
Total	123	20 (16.2%)	121	31 (25.6%)		

Table III

		Enemas				
Nursing			enokap .	Placebo group		
	54	14	(26%)	19	(35%)	
Nonnursing	68	6	(9%)	12	(18%)	
Total	122	20	(17%)	31	(26%)	

antidiuretic hormone elaborated during nursing may also play a role in regulating the thirst mechanism.2

Table IV illustrates the barium pattern distribution on serial radiographic studies. There appears to be no significant difference in the rate of progress of the barium between the placebo and the laxative medication in the patients studied. It is interesting to note that the column of barium arrived in the ascending colon in 3 patients at the end of one hour and at the end of 24 hours was in the large bowel in all patients.

The degree of urgency for a postpartum bowel movement should be re-evaluated if we consider intestinal physiology during this period. Two factors might be used to explain

Table IV. Barium pattern distribution

	1 hour		4 hours		24 hours		28 hours		32 hours	
	Placebo	Laxa-	Placebo	Laxa-	Placebo	Laxa-	Placebo	Laxa- tive	Placebo	Laxa-
Stomach	3	7	1	1	0	0	0	0	0	0
Small bowel	11	10	2	6	0	0	0	0	0	0
Jejunum	4	8	0	1	0	0	0	0	0	0
Ileum	7	2	2	5	0	0	0	0	0	0
Large bowel	3	1	11	11	22	14	17	17	17	21
Cecum	1	0	1	4	0	1	0	0	0	0
Ascending colon	2	1	7	4	4	3	4	3	3	3
Transverse colon	0	0	2	3	6	5	5	4	6	5
Descending colon	0	0	1	0	6	4	5	3	5	5
Sigmoid	0	0	0	0	3	0	2	3	2	4
Rectum	0	0	0	0	2	1	1	4	1	4
Eliminated	0	0	0	0	1	1	0	2	2	3

the increased demand of the primiparous patients for an enema: the larger episiotomy with accompanying discomfort and fear of having a bowel movement plus longer labors with associated relatively greater dehydration.

The figures in this study agree with other figures in the literature concerning postpartum bowel therapy1, 3-5 but adds to it the fact that a placebo yields about the same results as any regimen that is tried. It seems apparent that time is the single essential factor which best establishes physiologic postpartum bowel function irrespective of what is used as a laxative medication. The postpartum enema should be reserved for those patients who need and request it. It would seem advisable that physicians as well as nurses should aid in the reduction of the patient's anxiety and reduction of the traditional attitude that postpartum bowel function is physiologic and not pathologic. Other measures that may well promote return of physiologic bowel function are ambulation, adequate hydration, and control of episiotomy discomfort.

Summary

- A double-blind study of postpartum bowel function was carried out on 244 patients.
- 2. No apparent difference in effect was seen between the placebo and the laxative medication.

- 3. Primiparous patients requested more enemas than did multiparous patients.
- 4. Lactating patients requested more enemas than did nonlactating patients.
- 5. Serial radiographic determinations were carried out on 20 postpartum patients. No apparent difference was noted between the group receiving placebos and the group receiving laxative medication. The barium was located in all patients in the large colon at the end of 24 hours.
- 6. Time appears to be the main factor that promotes a restoration of physiologic bowel function.

Appreciation is extended to Dr. Ruppert Powell for the radiographic interpretations and to Mrs. Ruth Whitmer and the nursing staff of the Department of Obstetrics for their valuable assistance in this study. I also wish to thank the Purdue-Frederick Co. for the medication used in this study, Senokap.

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Cesarean section complicated post partum by volvulus

Report of a case and review of the literature

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MAJOR surgical complications occur in the postpartum phase and constant awareness of their coexistence must be maintained. When intestinal obstruction occurs in the late antepartum or early postpartum stage the typical symptoms and signs can be masked. Delay in diagnosis, indecision, or unreasonable conservatism are perilous. Intestinal obstruction associated with pregnancy occurs about 1 in 50,000 cases, and in a hospital where 2,500 deliveries are conducted each year the complication would occur once in 20 years.

Mrs. E. H., a 34-year-old para 2-0-0-2, was delivered at the Beth-El Hospital on Aug. 11, 1957, via a low cervical cesarean section because of a large fetus. A transverse incision was made in the lower uterine segment. The baby weighed 4,300 grams and was delivered in good condition. On the third postoperative day, nausea, vomiting, and mild abdominal distention occurred associated with a sudden onset of severe constant abdominal pain. The patient was treated with intravenous alimentation and intubation. Rectal irrigations resulted in a small amount of feces and flatus. A roentgenogram of the abdomen disclosed distention of the small bowel and some gas in the large intestine. In the next 24 hours there was no success in the passage of the intestinal decompression tube and the abdomen became more distended.

Physical examination revealed the presence of a tender, cystic movable mass approximately 4 to 5 cm. in the right upper quadrant. (A cholecystectomy was performed in 1951.) Laparotomy was carried out on August 16 and a twist of the cecum, approximately 180 degrees in a counterclockwise fashion, was found. The cecum was dilated 4 to 5 times its normal size and an adhesive band was present at the site of the previous cholecystectomy. There were yellow-green discolored areas in the intestinal lining, and its wall was extremely thin. There was uniform dilatation of the small intestine but no point of collapse in the large bowel. The previous operative incision in the uterus was covered completely by the bladder flap and there was no reaction or infection in it. The volvulus was untwisted, adhesions lysed, and a cecostomy performed. The patient recovered. Subsequent history disclosed that the patient had frequent episodes of upper abdominal pain associated with nausea, vomiting, and constipation but recovery was always spontaneous in 24 hours.

Comment

Jellinghaus,⁴ in 1932, reported on a 38-year-old para 1-0-0-1 who had a cervical cesarean section. The patient's postoperative course was uneventful until the sixth day when a sudden, severe pain developed in the right upper quadrant. A loop of intestine was visualized and palpated in that area. A laparotomy was performed and a volvulus

From the Departments of Obstetrics and Gynecology, Beth-El Hospital and the State University of New York, Downstate Medical Center, College of Medicine. was found in the distal part of the ileum. The affected area rotated 180 degrees clockwise and it was bluish red. The volvulus was turned in the opposite direction and gas was squeezed into the cecum. The patient recovered. Jellinghaus4 believed that volvulus was a nonpreventable surgical complication. In 1954 Brock1 reported an instance of volvulus of the cecum which occurred 10 days after a cesarean section in a para 1-0-0-1 who previously had intestinal obstruction after her first cesarean section. In his case, perforation occurred and a right colectomy was performed followed by an end-to-end ileotransverse colostomy. The patient recovered. Brock1 stressed the diagnostic value of the roentgenogram which revealed a massive gas-filled loop of bowel in one of the quadrants of the abdomen. No gas was seen in the descending or transverse colon in volvulus of the cecum whereas these portions of the colon are distended in sigmoid volvulus. Instillation of barium into the colon will demonstrate a collapsed but patent descending and transverse colon as the point of obstruction always is adjacent to the large affected segment.

Harer and Harer³ reviewed the world literature on volvulus complications of pregnancy and found 112 cases, of which 18 were reported from the United States. These authors stated that volvulus was the most common cause of postpartum intestinal ob-

struction. Only 25 per cent of the cases reported had the correct preoperative diagnosis. The sigmoid was the most common site and the cases were concentrated in the third trimester. The age of the mother exerted no apparent influence on the disease but an increase in parity predisposed to volvulus, possibly because of relaxation of the abdominal wall musculature. Most cases occur at term or intrapartum when the abdomen is distended by the pregnant uterus, although torsion of abdominal contents at that stage of gestation would seem most difficult. The degree of volvulus varied from 180 to 800 degrees and there was a greater incidence in the counterclockwise twist. The condition of the intestine may be in any stage between slight engorgement to gangrene or perforation. The maternal mortality rate reported by Kohn and associates⁵ was 25 per cent and by Harer and Harer³ 31 per cent.

Considerable distention must be present before the relaxed abdominal wall of the postpartum patient becomes tense. The persistence of dilated loops of bowel after routine measures for relief of postpartum ileus should alert the physician to the possibility of obstruction, particularly if there was no previous operation. Early diagnosis, prompt decompression, and the proper maintenance of electrolyte balance are imperative.

Cannell and Toyee² observed 10 cases of

Table I. Cesarean section and postpartum volvulus

Author	Year	Age	Parity	Day post partum	Site of volvulus	Type of operation
Jellinghaus ⁴	1932	38	1-0-0-1	6	Ileum	Untwisted loop
Brock ¹	1954	35	1-0-0-1	10	Cecum	Perforation; colectomy; end- to-end ileo transverse colostomy
Cannell and Tovee ²	1957		Not stated	2	Site undetermined	None; knee-chest position and elevation of uterus
		35 (Not stated 2 other cases	10 reported	Cecum but no details)	Cecostomy; lysis of adhesions
Harer and Harer ³	1958	31	3-0-1-2	16	Ileum	Gangrene; resection and end-to-end anastomosis
Present study	1959	34	2-0-0-2	4	Cecum	Cecostomy; lysis of adhesions

postpartum intestinal obstruction of the large bowel, and in 4 cases volvulus was present. In each instance a previous cesarean section had been performed. The data on 2 of these cases was insufficient for analysis. In 1958 Harer and Harer³ reported on a para 3-0-1-2, aged 31, whose fourth pregnancy was terminated by a low cervical cesarean section in the thiry-eighth week. The fifth pregnancy was normal until the thirtyseventh week, when the uterus ruptured. A supracervical hysterectomy was performed after the delivery of a live female infant. The patient was discharged on the ninth postoperative day, but was readmitted 7 days later with sudden, severe, constant upper abdominal pain that radiated to the back. Roentgenograms disclosed evidence of intestinal obstruction. At laparotomy a volvulus was present with gangrene in the involved segment of the ileum. A band of adhesions was found at the site of the volvulus. Resection of 110 cm. of small bowel was performed followed by an endto-end anastomosis. The patient recovered. (Two other patients reported by them who had volvulus at the time of cesarean section are not included in the present study.)

Five previously reported cases and one of our own cases were summarized (Table I). The median age of the patients was 35 years. Two of the women had one previous pregnancy, another had 2, and the fourth had 3 term gestations. In 2 instances the parity was not stated. The symptoms in all 6 cases were a sudden, severe onset of abdominal pain, and in 4 of the 6 patients physical examination disclosed a tender palpable abdominal

mass. Roentgenogram was diagnostic of mechanical intestinal obstruction in 4 cases where films were made but volvulus was diagnosed in only one of them. The complication occurred on the second, fourth, sixth, and sixteenth postoperative days, respectively, in 4 patients and on the tenth postoperative day in 2. The operative findings revealed a volvulus of the ileum in 2, and of the cecum in 3. In one patient no operation was performed. The woman was placed in the knee-chest position, the uterus was manipulated anteriorly, and the intestine became audibly deflated immediately. The crampy abdominal pain ceased at once and 48 hours later the patient passed feces and flatus spontaneously. The operations varied from merely untwisting a loop (which cured one of the patients) to an additional cecostomy with lysis of adhesions in 2 others. The fifth patient developed a perforation of the intestine prior to operation, and a colectomy with an end-to-end anastomosis was performed. In the sixth case the involved segment developed gangrene and resection anastomosis was required.

Summary

- 1. A review of 5 previously published cases of volvulus after cesarean section was reported. A sixth case was added.
- 2. A tender abdominal mass was palpable in 4 of the 6 women.
- 3. The type of corrective operation varied from a simple untwisting of the involved segment to resection of gangrenous loop of intestine.
 - 4. All patients recovered.

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Oxygen administration to the mother and its relation to blood oxygen in the newborn infant

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With the technical assistance of

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THE oxygen environment of the human fetus in utero on the one hand, and shortly after its birth on the other hand, is poorly understood despite many attempts at clarification. The methodology involved in measuring oxygen is complex, time consuming, and fraught with pitfalls. In addition, different methods may yield different results or are open to different interpretations. Indeed, the analytical calculations used in the investigation reported here must be corrected by a factor so critical that it depends on the day-to-day variation in the barometric pressure. Maternal-fetal oxygen relationships are complicated, and in the human it is impossible under any available conditions to acquire the necessary material for complete understanding. For example, it would be desirable to make simultaneous determinations of maternal and fetal arterial and venous blood hydrogen ion concentration, partial pressure of oxygen (pO₂), partial pressure of carbon dioxide (pCo₂), oxygen content, and oxygen capacity. In addition, we should know the uterine blood volume and rate of flow at the instant the samples are taken.

To study the human in this field it is obviously necessary to make material com-

promises and work with suboptimal sampling. Considerable information may be obtained by measuring one of the variables mentioned above under proper conditions. Fetal blood, normally resistant to alkali denaturation and containing little carbonic anhydrase (to mention only two of its many differences from maternal blood), undoubtedly handles oxygen considerably differently than maternal blood does. Although the basal metabolic rate of a newborn infant may be as low as 19.5 calories per square meter per hour, it is generally agreed that the higher the oxygen in the infant's blood at the time of delivery, the better the baby's chance for a satisfactory survival.

Adult arterial blood normally contains about 0.25 ml. of O₂ and 1.04 ml. of N₂ per 100 ml. in physical solution (dissolved). About 19 ml. of additional O₂ is transported in chemical combination with hemoglobin. Behnke¹ has shown that by administering O₂ to the adult human through a face mask, it is possible to replace blood N₂ with O₂.

The oxygen dissociation curve is a graphic representation of the relation between the quantity of O_2 available for combination with hemoglobin and the amount of O_2 combined with hemoglobin. Because the O_2 dissociation curve is flat at its upper end most of the additional blood O_2 obtained by replacing N_2 with O_2 must be carried in simple solution and not in combination with hemoglobin. Normally, the quantity of dissolved oxygen is so small it is of no practical im-

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portance to the mother but may be important to the fetus. Assuming that blood arriving to the fetus from the placenta is about 50 per cent saturated with O2, 10 ml. of O2 per 100 ml. of blood is available to the fetus. Replacement of the dissolved N2 in maternal blood with O2 might present to the fetus an additional 1 ml. of O2 per 100 ml. of blood. Of greater importance is the increase in O₂ combined with hemoglobin. Because the slope of the newborn infant's oxygen dissociation curve in the 50 per cent oxygen saturation range is great, a small increase of O2 in this portion of the curve results in a large increase in oxyhemoglobin.

Material and methods

This is a report of a continuing investigation² in which O₂ is administered at a rate of 10 L. per minute through a BLB mask (commonly used in high altitude flight) to the woman in labor. The BLB mask was chosen deliberately after a study, lasting several months, was made of the manner in which various types of "demand masks" fitted the face of a woman undergoing contortions associated with labor. No single mask was satisfactory for use on every patient. The BLB mask usually fitted satisfactorily, a condition which must obtain if the highly concentrated nitrogen of alveolar air is to reach gaseous equilibrium with the small amount of nitrogen in the "dead space" of the mask and be blown out of the mask as the woman exhales. Because a loose-fitting mask has what amounts to an N2 leak, all patients were attended continuously after the mask was applied. Each of the patients in the present series was delivered vaginally; none had a general anesthetic, and all deliveries were "normal."

A segment of umbilical cord, clamped before the infant breathed or cried, was immediately removed between clamps. Umbilical vein blood was at once drawn anaerobically into a 10 ml. greased syringe previously rinsed with heparin. Determination of the pO₂ was done with a modified Riley technique checked by analyzing blood exposed to known gas tensions. All analyses were completed within 15 minutes after the birth. Duplicate analyses were done and the results which agreed within 4 mm. Hg were averaged to obtain the final answer. The result of a blood analysis was accepted for inclusion in this series only if: (1) labor was normal and did not progress so rapidly that oxygen could not be given, (2) the mask fitted the face and did not leak until the moment of delivery, (3) the patient tolerated the mask, (4) the birth was conducted with no anesthesia or with pudendal block, (5) the cord was clamped before the baby breathed or cried, (6) sufficient nonclotting umbilical vein blood was available for duplicate analyses, and (7) duplicate blood analyses agreed within 4 mm. Hg. The Riley method is one type of direct blood gas analysis which depends on the equilibration of a bubble of gas with blood at body temperature and the subsequent analysis of the bubble for CO2 and O2. The gas used is a mixture containing 82 per cent nitrogen, 12 per cent oxygen, and 6 per cent carbon dioxide. Equilibration and measurement of the gas bubble is done in a constant temperature water bath with a tuberculin syringe to which is fused a calibrated capillary tube. Following equilibration of the bubble with blood, carbon dioxide is absorbed with 0.1 ml. normal sodium hydroxide, and oxygen is absorbed with alkaline hydrosulfite. Since the partial pressure of a gas is proportional to its partial volume and the bubble length is measured with a telescope before and after each gas is absorbed, the pO2 and pCo2 may be calculated. Approximately one year is required to set up and standardize the procedure for routine use in a laboratory.

The control group consisted of babies of mothers who did not receive oxygen but whose clinical management was comparable to that of the experimental group.

Results

The average umbilical vein pO2 of the 45 controls is 28.5 mm. Hg. Although the range is 10 to 55 mm. Hg, the vast majority are rather tightly grouped about the average. Of the 80 women who received O2 (Table I),

Table I. Partial pressure of oxygen in umbilical vein blood of infants whose mothers received oxygen prior to delivery

Minutes O. given	No. of patients	pO2 average (mm. Hg)
10 or less	51	31.0
11 to 15	11	34.4*
More than 15	18	40.0*

*Only two fell below average.

51 received it for 10 minutes or less, 11 for from 11 to 15 minutes, and 18 for more than 15 minutes. There was no significant difference between the control group and the group receiving O₂ for 10 minutes or less. The average pO₂ of the "11 to 15 minutes" group was 34.4 mm. Hg, with two determinations falling below average. The average pO₂ of the "over 15 minutes" group was 40 mm. Hg, with two determinations falling below average. Thus, the average of

the "11 to 15 minutes" group was 21 per cent above that of the control group and the average of the "more than 15 minutes" group was 40 per cent above that of the controls. There was no direct linear relation between the time O₂ was administered and the umbilical vein pO₂.

Conclusions

Babies born of mothers who receive O₂ for more than 10 minutes prior to delivery have a considerable increase in available O₂ compared to babies of mothers who receive no O₂.

Although an increase in the O₂ available to the fetus may be lifesaving in certain pathologic conditions, whether or not O₂ is of benefit during a "normal" labor must await analysis of the clinical outcome of a large series of babies from mothers treated with O₂.

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Discussion

Dr. George A. Saxton, Jr., Chicago, Illinois. As Dr. McClure states, supplementary oxygen does not seem to be necessary under normal circumstances. Between uterine contractions, the mother hyperventilates and raises her own oxygen values.

What, then, are the indications and what are the limitations of supplementary oxygen? If drugs that suppress respiration are required, additional oxygen may be indicated. Also, one should consider the position of the mother during labor. The work with animals reported by Dr. Irwin Kaiser's group in Minnesota showed how difficult it was to maintain normal arterial oxygen saturation in pregnant ewes if they were lying on their sides during delivery. I would like to know what happens, therefore, to arterial oxygen saturation of the mother when she is lying supine, inclined 45 degrees, or is in the Sims position. Pulmonary disease would also be a very important indication for oxygen.

Convincing evidence that the normal fetus does not require supplementary oxygen, although its blood is markedly unsaturated, is revealed in the work of Kaiser and Cummings on goats and ewes. They found that in the last 10 days of gestation, the goat fetus is capable of increased hematopoiesis if the mother is subjected to low oxygen breathing. The normal fetus does not increase its hematopoiesis despite the fact that its arterial blood is unsaturated. Miller and his group in Atlanta and in Stockholm have demonstrated that the newborn infant with asphyxia pallidum can survive at very low oxygen tensions, especially if CO₂ is permitted to accumulate.

One should never have a false feeling of security that he can store oxygen in a patient by administering it for 10 or 15 minutes or for an hour. There is no way that we can store oxygen in the body. It has to come through the mother and the placenta continuously. The heart and lungs of the mother must be watched carefully to be sure of normal function. If there is sudden

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oy in en er ad ly failure of the circulation or ventilation, therapeutic measures are required within 2 to 3 minutes. The administration of supplementary oxygen is one of these measures.

In conclusion, then, it would seem unnecessary to use supplementary oxygen routinely but important to have it readily available for immediate use whenever there is any question regarding the adequacy of maternal ventilation, cardiac function, or the integrity of placental blood supply.

DR. McClure (Closing). The statement has been made in the obstetric and gynecologic literature that every patient about to be delivered

should have prophylactic oxygen. I am not quite willing to go that far. As Dr. Saxton pointed out, there is no sharp evidence that the patient needs oxygen. On the other hand, it is impossible to tell by current methods when a baby is in distress during the last 5 or 6 minutes before delivery. Nor do we know what happens in the first 5 or 6 minutes postnatally. I am convinced that the administration of oxygen will not do the baby any harm but certainly in some instances it may do the baby a tremendous amount of good. I, therefore, am willing to continue my "prophylactic oxygen" series for a bit to determine if there is any improvement in the survival rate among the newborn infants.

The electronic evaluation of fetal heart rate

III. The effect of an oxytocic agent used for the induction of labor

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LABOR in itself is an added stress for the fetus. Evidence exists that uterine contractions, basic in the process of labor, may result in varying degrees of interference with placental circulation.1-4 Under normal conditions the volume of blood flowing through the placenta is more than adequate to supply the oxygen requirement of the fetus, and labor is usually well tolerated.1, 2, 4-8 However, under other circumstances when the amount of maternal-fetal exchange is borderline or when abnormal types of uterine contractions occur, a transitory additional reduction in blood flow may effect poor oxygenation of the fetus. Manifestations of fetal distress may ensue and be reflected by alterations of the fetal heart rate.9-11

Knowledge, therefore, of the normal limits of fetal cardiac response to physiologic contractions may be of value in appraising the ability of a given fetus to tolerate labor. A clear definition of pathologic deviations may consequently aid in the early recognition of unfavorable fetal environment.

For well over 50 years fetal bradycardia and irregularity have been considered of importance in the assessment of fetal wellbeing.¹²⁻¹⁸ While the present criteria have been of value in the management of fetal distress, the disadvantages of periodic stethoscopic sampling and the inherent human counting error have limited somewhat its accuracy.¹⁹

With the use of electronic techniques for continuous monitoring, it is now possible to have an objective measurement of fetal heart rate under the various conditions of labor. This method is advantageous since it provides recorded information of the instantaneous heart rate from which patterns of beat-to-beat cardiac activity are discernible for analysis.

In recent years the widespread use of oxytocics for the induction of labor is adequate testimony to their efficacy. 20-24 However, the injudicious use of these drugs may produce abnormal uterine activity and possible compromise of the fetal environment. 25-80 It may be of some importance, therefore, to determine if there are any fetal heart rate deviations when labor is being so induced. An unusual pattern of response to infrequent or physiologic contractions may be indicative of borderline inadequacy of maternal-fetal circulation.

It is the purpose of this report to describe fetal heart rate patterns that have been observed during oxytocin-induced labor.

Patients and procedures

Of the 40 patients in this study who were admitted to the Grace-New Haven Community Hospital at or near term, the records of 11 have been selected as representative of

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*Markle Scholar in Medical Science.

the fetal heart rate patterns associated with oxytocin induction of labor.

The oxytocin was administered by the intravenous drip method whereby 10 units of the agent was added to 1,000 ml. of 5 per cent dextrose in water and the dose regulated until uterine contractions ensued.

In the majority of patients the frequency and duration of uterine contractions were determined by abdominal palpation and correlated with changes in the fetal ECG base line. In some patients (58-266, 58-279, 58-274, 58-230) transabdominal aminocentesis was performed. Following the introduction of a small caliber polyethylene tube, the amniotic fluid pressure was determined by means of a Stratham strain gauge and an appropriate four-channel Edin recorder.

The fetal heart rate was recorded with the electronic techniques previously described^{31, 32} and is presented as an instantaneous rate-time graph plotted on a semilogarithmic scale.

Results

In this limited study of 40 patients, the effect of uterine contractions on fetal heart rate appeared to be influenced largely by the frequency, duration, and intensity of uterine contractions. The probability that, in some instances, this was modified by maternal status such as age, hypotension, pre-eclampsia, anemia, etc., was given consideration.

Fetal heart rate patterns versus frequency and duration of contractions. In Fig. 1, A, where uterine contractions are occurring at the rate of about 4 per 10 minutes and lasting 40 to 60 seconds, the fetal heart rate is relatively unchanged. Fig. 1, B, illustrates a similar situation. In this case the amniotic fluid pressure shows a peak intensity of 60 to 70 mm. Hg with about 8 to 10 mm. Hg tonus between contractions.

Toward the end of the tracing in Fig. 2, A slight fetal cardiac irregularity and tachycardia are noted about 5 minutes after a contraction lasting about 80 seconds which was followed in about 70 seconds by another contraction of similar duration. The last 2 contractions of Fig. 2, A are of shorter duration with a longer interval between. Note absence of tachycardia a few minutes after the contractions become less frequent and of shorter duration.

The contractions shown in Fig. 2, B are occurring at the rate of 4.5 per 10 minutes; however, in the center of the tracing there are 5 contractions in the space of 8 minutes. The peak amniotic fluid pressure is 60 to 70 mm. Hg and the tonus about 10 mm. Hg. A slight acceleration in rate is present toward the end of the tracing.

Fig. 3, A shows the bradycardia and mild tachycardia associated with frequent uterine contractions. In some patients tachycardia alone is seen, whereas in others, bradycardia is also present even though the contractions are of similar frequency and duration. (This patient had mild hypertension.) Note the beginning of bradycardia toward the end of a uterine contraction.

The uterine contractions shown in Fig. 3, B are occurring at the rate of 4.5 per 10 minutes and have a peak amniotic fluid pressure of about 75 to 80 mm. Hg and a tonus of about 20 mm. Hg. As shown in Fig. 3, A, the onset of the bradycardia is toward the end of the contraction. Mild tachycardia follows the bradycardia and the slowing of the fetal heart rate lessens as the interval between contractions becomes longer.

Fetal heart rate patterns with "tetanic" uterine contractions. At the beginning of the tracing shown in Fig. 4, A, an oxytocic infusion was started. The patient was very sensitive and almost immediately had a "tetanic" uterine contraction. Since this was timed by abdominal palpation, the exact duration is not known. The mild tachycardia and irregularity followed by marked bradycardia and irregularity are seen readily. Tachycardia and irregularity followed the episode of bradycardia.

Although the uterine contractions shown in Fig. 4, B are of less than average amplitude, the tonus for the first part of the tracing is higher (15 to 20 mm. Hg) than usual (10 mm. Hg). Bradycardia and slight irregularity were associated with this part of the record.

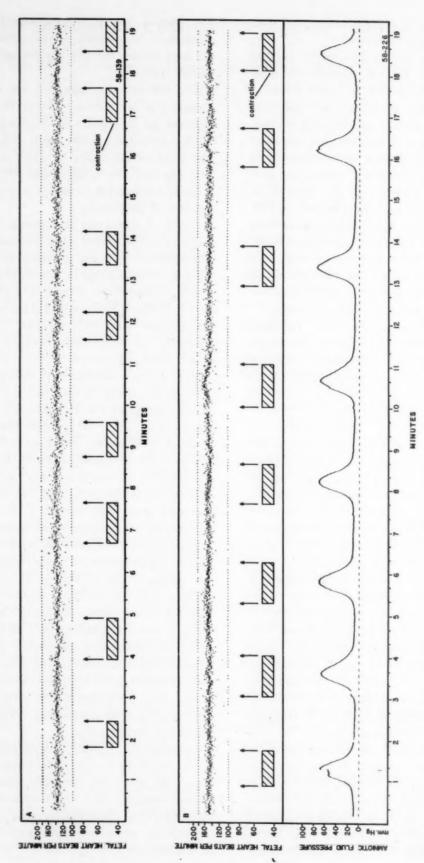


Fig. 1. A, Relatively unchanged fetal heart rate associated with uterine contractions occurring about 4 per 10 minutes. B, Situation similar to that of A. Amniotic fluid pressure shows peak amplitude of 60 to 70 mm. Hg and a tonus of 8 to 10 mm. Hg.

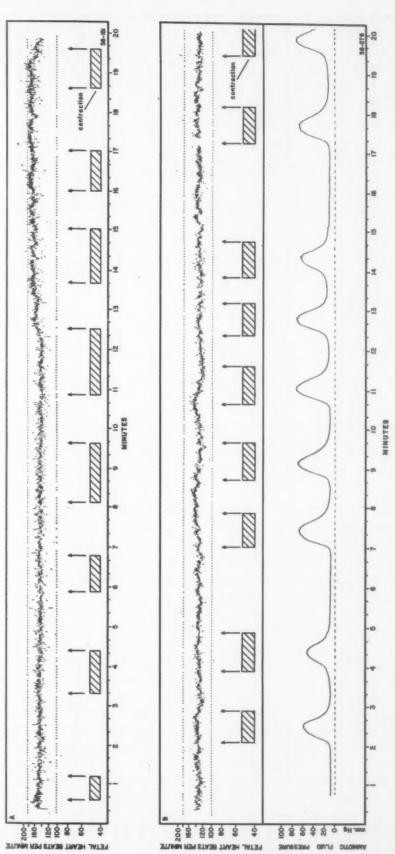
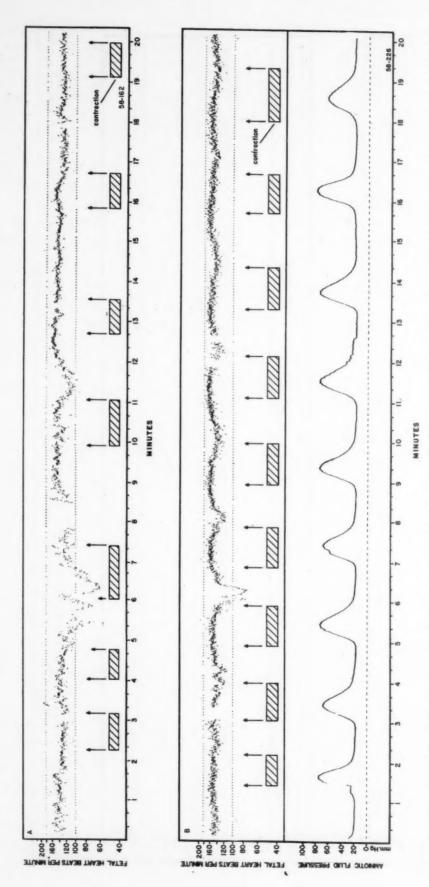


Fig. 2. A, Slight fetal cardiac irregularity and tachycardia (end of tracing) following contractions of 80 seconds' duration with a 70 second interval between. Note absence of tachycardia a few minutes after the contractions become less frequent and of shorter duration. B, Slight fetal tachycardia following 5 closely spaced contractions. Peak amniotic fluid pressure, 60 to 70 mm. Hg; tonus about 10 mm. Hg.



contraction. B, Bradycardia intermixed with tachycardia. As the contractions become less frequent, the bradycardia lessens. Note, as in A, the onset of bradycardia toward the end of the uterine contraction. Fig. 3. 4, Bradycardia followed by mild tachycardia associated with frequent uterine contractions. Note onset of bradycardia toward the end of the uterine

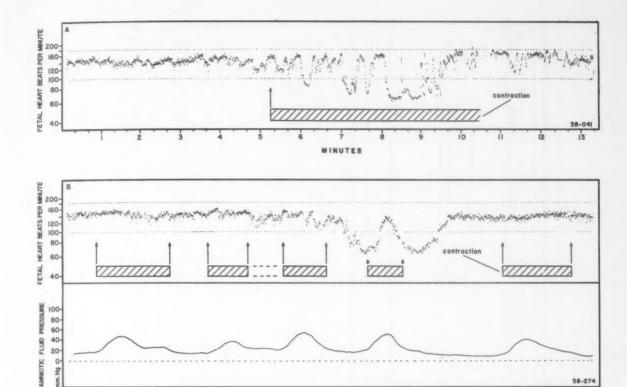


Fig. 4. A, Severe bradycardia and irregularity preceded and followed by tachycardia and irregularity associated with a "tetanic" uterine contraction just after oxytocin induction was started. B, Note bradycardia and mild irregularity occurring a few minutes after elevation of uterine tonus to about 20 mm. Hg (usually 8 to 10 mm. Hg).

MINUTES

Fetal heart rate patterns with questionable variation in fetal reserve. Figs. 1 to 4 are considered generally representative of the patients in this study. Figs. 5 and 6 were unusual responses to induction and are indicative of variations in fetal reserve. Although the contractions noted to be of marked intensity in Fig. 5, A are occurring at the rate of 4.5 per 10 minutes, the fetal heart rate is unchanged except for a slight irregularity. In Fig. 5, B 10 contractions occur in the last 13 minutes of the tracing and the tonus is about 20 mm. Hg. The fetal heart rate shows only mild irregularity and slight tachycardia. At delivery both infants were in good condition.

The first 10 minutes of the record of Fig. 6, A was recorded from a pre-eclamptic patient with a blood pressure of 190/130. At the division in the record she was given 20 mg. of Reserpine intramuscularly. Twenty minutes later the irregularity and tachycardia noted in the earlier tracing had completely disappeared as shown in the last portion of Fig. 6, A. A few hours later induction was started. Although the contractions were mild and of short duration, fetal bradycardia became profound. Because the fetus tolerated labor poorly, a cesarean section was performed for pre-eclampsia. The baby weighed 3,175 grams and was in poor condition with an Apgar score of 6. The amniotic fluid was stained heavily with recent meconium.

Fig. 6, C is a record of the fetal heart rate pattern of a pre-eclamptic patient with a blood pressure of 160/95 at 43 weeks of gestation. The mild irregularity and tachycardia preceding bradycardia which was in turn followed by sustained tachycardia are seen clearly. The contractions at this time were mild. At cesarean section the 3,200 gram infant was cyanotic and limp with an

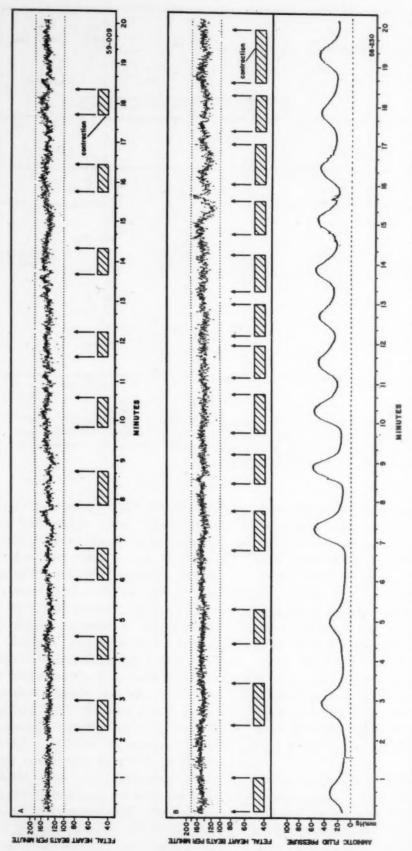


Fig. 5. A, Contractions occurring at the rate of 4.5 per 10 minutes. The fetal heart rate is relatively unchanged except for slight irregularity. B, In the last 13 minutes of the tracing there are 10 uterine contractions with a high tonus (20 mm. Hg). The fetal heart rate shows mild irregularity and slight tachycardia. This fetal heart rate pattern and that of A are unusual with frequent uterine contractions.

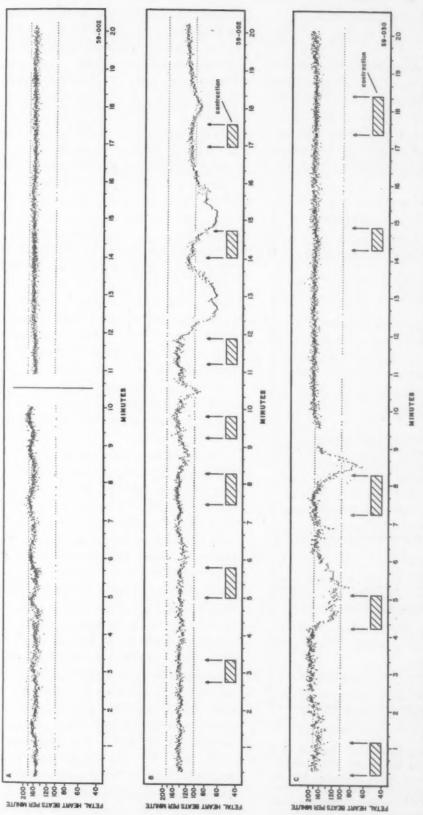


Fig. 6. A, Fetal irregularity and mild tachycardia noted in a pre-eclamptic patient with a BP 190/130. At the separation of the two portions of the tracing, 20 mg. of Reservine was given intranuscularly. Twenty minutes later the irregularity and tachycardia had disappeared. B, Same patient as in A. Note progressively developing bradycardia even though contractions are of short duration. Because of the poor fetal tolerance of labor, a cesarean section was performed. At delivery the fetus was in poor condition and the anniotic fluid heavily stained with recent meconium. C, Mild fetal irregularity and tachycardia preceding bradycardia which is followed by sustained tachycardia in a pre-eclamptic patient at 43 weeks of gestation. Note infrequent uterine contractions. At cesarean section the fetus was cyanotic and limp and covered with fresh meconium.

Apgar score of 2. The amniotic fluid was stained heavily with fresh meconium.

Comment

From this study of patients who were receiving an oxytocic agent for the induction of labor, certain deviations were observed in fetal heart rate in relation to frequency, duration, and intensity of uterine contractions. In the majority of patients (of which Figs. 1 to 4 are representative), when the

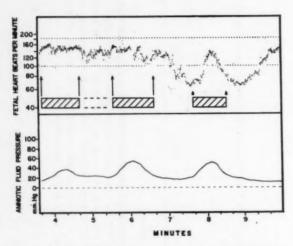


Fig. 7. The relationship of fetal bradycardia to prolonged uterine contraction and persistent elevation of uterine tonus following oxytocin induction of labor (58-274).

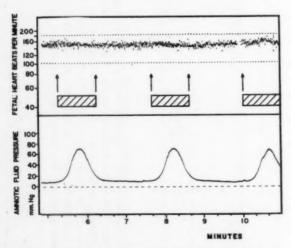


Fig. 8. Pattern of fetal heart rate observed in a normotensive patient in association with contractions simulating normal labor induced by the administration of oxytocin intravenously. Note uterine tonus remains within normal limits usually encountered in the interval between contractions (58-266).

contractions were occurring at the rate of 3 to 4 per 10 minutes, only minor deviations in fetal heart rate were noted. These were of no apparent detriment to the fetus even though slight tachycardia and transitory bradycardia were occasionally present. In this group of patients without known complications when the oxytocin was given so that the contractions of the type encountered in "normal" labor were simulated, no significant deviations in fetal heart rate were noted (Fig. 1, A and B). Among those patients in whom more frequent contractions followed the administration of the oxytocin, greater alterations of the fetal heart rate were observed. If approximately 3 closely spaced contractions of 60 to 80 seconds' duration (Figs. 2, A and B and 3, A and B) occurred, there was usually mild tachycardia and irregularity which was followed occasionally by mild bradycardia. With a "tetanic" uterine contraction profound bradycardia usually occurred (Fig. 4, A and B). Uterine hypertonus appeared to have a marked effect on fetal heart rate even though the amplitude of the individual contractions was less than average (Fig. 7).

In a much smaller group of patients, of whom Fig. 5, A and B is representative, even though contractions of strong character occurred very frequently, only minor deviations in fetal heart rate were noted. This usual lack of effect on fetal cardiac activity may denote an above average competency of the maternal-fetal vascular system. On the other hand, the tachycardia and marked bradycardia associated with infrequent contractions in the two pre-eclamptic patients whose tracings are shown in Fig. 6, A, B, and C may reflect compromised fetal reserve. The depressed condition of these infants at birth also supports this idea. A sharp contrast was observed in the effect of mild contractions on the fetal heart rate in the pre-eclamptic patient (Fig. 8) and in the normotensive patient (Fig. 9). The possibility of careful oxytocic infusion being used as a test for placental function in toxemic and diabetic patients who are at or near term and in postterm patients is being evaluated.

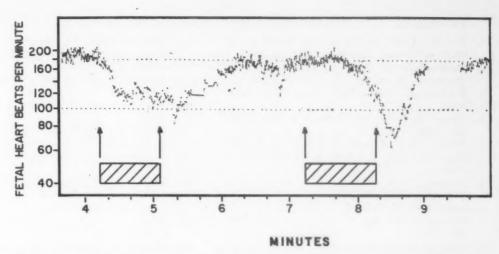


Fig. 9. Fetal bradycardia associated with induction of mild and infrequent contractions in a patient with pre-eclampsia. Note tachycardia and irregularity preceding bradycardia (59-030).

In a recent report Hon³³ suggested that fetal bradycardia noted late in the contraction phase and associated with frequent and strong uterine contractions was probably "hypoxic" in origin. The bradycardia observed in this study is of this type and is occasionally preceded and followed by mild tachycardia.

Previous studies of the hemodynamics of uterine contractions show that maternal blood flow through the intervillous space is impeded and may be cut off entirely at the height of the contraction, and, if uterine hypertonus is present, this space may be physiologically isolated and fetal oxygen reserves depleted.^{2, 3, 9, 10}

It would seem, therefore, that while controlled intravenous infusion of an oxytocin is an excellent method of inducing labor, its use should be supervised carefully as it may be potentially capable of interfering with fetal oxygenation, particularly under circumstances where fetal circulatory reserve may be compromised by maternal age, preeclampsia, maternal hypotension, and perhaps, postmaturity.

Summary

1. In a limited study of 40 oxytocin-induced labors, deviations in fetal heart rate were noted if the induction was too rapid.

- 2. Fetal tachycardia preceding and following bradycardia was observed usually if 3 contractions of 60 to 80 seconds' duration occurred in 6 to 7 minutes.
- 3. Profound bradycardia and irregularity were noted with "tetanic" uterine contractions
- 4. A small number of patients showed only minor fetal heart rate deviations even though labor was being rapidly induced.
- 5. The ECG of the fetuses of 2 preeclamptic patients showed marked bradycardia associated with infrequent, mild uterine contractions.
- 6. The fetal bradycardia noted in this study occurred late in the contraction phase and may be primarily hypoxic in origin.
- 7. The fetal heart rate pattern associated with oxytocin induction may provide an index of fetal reserve.

Conclusion

While oxytocin infusion is a good method of inducing labor, it may produce marked fetal bradycardia if used injudiciously.

We wish to thank George Park, Jean Peterson, R.N., Margaret Ranek, R.N., Linda Klebanoff, and Jane Dick, whose research and technical assistance have made this study possible.

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Influence of postspinal hypotension on the fetal electrocardiogram

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DURING the past few years, reports have appeared containing accounts of the successful use of spinal anesthesia in thousands of obstetrical cases without serious maternal complications.1, 2 What of the fetus? It is generally accepted that if maternal circulatory depression is avoided, spinal anesthesia has no deleterious effect on the fetus. Hypotension, however, occurs so frequently during spinal anesthesia for cesarean section that our first impression would be that this technique might jeopardize the infant. A recent indictment of spinal anesthesia for cesarean section³ states "hypotension in the mother is a constant threat (with spinal anesthesia) and may cause hypoxia and damage to the fetus." Wylie4 has stated that maternal hypotension may lead to rapid fetal death. He believes that a maternal systolic blood pressure at or below 80 mm. Hg will lead to fetal anoxia within 5 minutes, and this opinion has been echoed by others. Clinically, the incidence of apnea neonatorum of 2 or more minutes is three times as frequent in elective cesarean section with patients under cyclopropane anesthesia as it is with spinal anesthesia. Phillips⁵ has shown in a clinical investigation of vaginal deliveries that the relative incidence of delayed respiration of the newborn is almost six times as great with general anesthesia as with spinal anesthesia. Pathologic changes of the central nervous system which result from hypoxia, however, need not be immediately apparent but may become evident as the infant grows older. Subtle and less dramatic changes, personality disorders, and behavioral problems may be the end result. The tolerance of the fetus to transient hypoxia has not been determined. We have not had defined the limits of a dangerous level of oxygen want, the level below which the incidence of irreparable fetal injury begins to increase. With this in mind, we have attempted to determine whether the hypotension associated with spinal anesthesia interferes with the oxygen supply to the fetus. At present, our most reliable index of intrauterine hypoxia is a bradycardia of 100 or less per minute.6 There is no indisputable proof that the cardiac rate in utero can predict what the future holds for a particular fetus. It is, however, the only parameter of value that can be objectively assessed in the as yet inaccessible fetus. Biaural auscultation of the fetal heart may be inaccurate and irregular and is subject to personal error. We have endeavored to explore this problem by means of continuous fetal electrocardiography prior to and following spinal anesthesia.

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Method

The following procedure was used to record the fetal electrocardiogram. The skin was cleansed with alcohol, and some Bentonite paste was rubbed into the skin. Standard ECG disk electrodes were attached with adhesive tape. Four recording electrodes were placed in the pattern of a square with sides 4 inches long. The first electrode was a midline epigastric lead, the second was to the left of midline, the third was a midline suprapubic lead, and the fourth was to the right of midline. An additional electrode was attached to the abdomen to ground the patient.

The primary apparatus requirements are very high amplification with a low noise level. We used a Grass polygraph with an EEG preamplifier. Recordings were generally taken at a sensitivity of either 50 or 30 μ v per centimeter. The noise level was about 3 μ v. The polygraph and operating table were grounded. Other sources of 60 cycle interference were also grounded.

We started our recordings with short trial runs, employing each of the 6 possible paired combinations of our 4 recording electrodes. The combination that gave the best fetal ECG was then used throughout the record-

ing session. For 90 per cent of our patients, the best combination of leads proved to be the midline epigastric-suprapubic one.

It should be noted that the maternal ECG is also present in most tracings of the fetal ECG obtained with abdominal leads (Fig. 1). However, the two different electrocardiograms are readily distinguished because of differences in amplitude and frequency. This procedure enabled us to detect instantaneous changes in the fetal heart rate and was satisfactory for our present research because we were interested in fetal heart rate changes during a short period of about 15 minutes.

The present study is based on 29 private and clinic patients scheduled for an elective cesarean section. All 29 were delivered of live infants.

Results

Fetal bradycardia was not observed in any of the 13 patients whose maternal systolic levels remained above 70 mm. Hg following the spinal anesthetic. The maternal hypotension was more extreme in 16 pa-

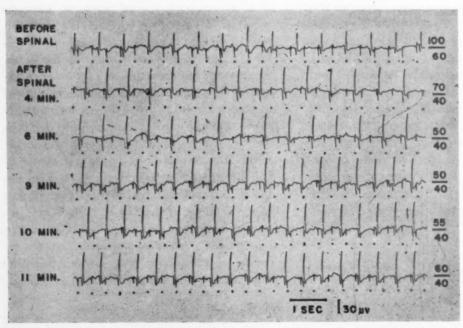


Fig. 1. Tracing of fetal and maternal electrocardiogram prior to and following spinal anesthesia for cesarean section. Fetal R waves indicated by small dots; overlapping of fetal and maternal complexes indicated by larger dots.

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tients and, in this group, the incidence of fetal bradycardia was proportional to the severity of the maternal hypotension (Table I). The U test of Mann and Whitney was employed to determine whether there was a statistically significant relationship between minimal maternal systolic level and incidence of fetal bradycardia. It was found that the probability of the observed relation occurring by chance was one in a hundred. Therefore, these data provide statistical support for the conclusion that fetal bradycardia is more likely to occur when the maternal systolic level drops to 60 mm. Hg or less. These data also suggest that fetal bradycardia due to maternal hypotension is unlikely when the minimum systolic level is between 70 and 100 mm. Hg. However, it should be noted that we had only 4 patients in that category. A larger number of patients would be required before one could state with confidence the critical maternal systolic level likely to precipitate fetal bradycardia. Another aspect of this question is whether the critical postspinal systolic level is different when the prespinal systolic level is unusually high, as for example in essential hypertension or toxemia of pregnancy. This, too, cannot be answered from our present

It is reasonable to assume that the occurrence of fetal bradycardia would depend on both extent and duration of maternal hypotension. An attempt was made to estimate the latter in terms of the time that the maternal systolic level remained below 80 mm. Hg. It was found that the occurrence of fetal bradycardia was related to duration of maternal hypotension (Table II). The Mann-Whitney U test revealed this to be statistically significant at the 3 per cent level of confidence. The small number of patients made it impossible to set any exact value on the critical duration. However, it may be noted that fetal bradycardia occurred only when the maternal hypotension had a total duration greater than 4 minutes and that thereafter the incidence of fetal bradycardia appeared to be proportional to duration of hypotension.

Table I. Relation between maternal systolic level and incidence of fetal bradycardia

Minimal maternal systolic pressure after spinal anesthetic (mm. Hg)	No. of patients	Incidence of fetal bradycardia (%)
100 or higher	9	0
90-99	1	0
80-89	0	0
70-79	3	0
60-69	5	20
50-59	8	38
Below 50	3	67

Table II. Relation between duration of maternal hypotension and incidence of fetal bradycardia

Duration of maternal systolic level below 80 mm. Hg (minutes)	No. of patients*	Incidence of fetal bradycardia
0-1.9	8	0
2-3.9	. 8	0
4-5.9	3	33
6 or longer	9	44

*One patient was omitted because data on duration were incomplete.

The times of onset of fetal bradycardia for the 6 patients involved were 8.5, 9, 10, 10, 10.5, and 11 minutes after the spinal anesthetic. For 5 of these patients, observations were sufficient to reveal that the onset of a maternal systolic level below 80 mm. Hg occurred 2 to 5 minutes after the spinal anesthetic. The delay between the onset of a maternal systolic pressure below 80 mm. Hg and onset of a fetal heart rate below 100 per minute was also determined for these 5 patients. This delay was 5, 5, 7, 8.5, and 9 minutes, respectively.

Conclusions

This study provides statistical evidence that the occurrence of fetal bradycardia is related to the extent and duration of maternal hypotension. Present data on 29 patients indicated an absence of fetal bradycardia due to maternal hypotension until the maternal systolic level dropped to 60 mm. Hg; thereafter, the incidence of fetal bradycardia was proportional to the extent of the maternal hypotension. Data on duration of hypotension indicated an absence of fetal bradycardia in patients whose systolic level remained below 80 mm. Hg for less than 4 minutes; thereafter, the incidence of fetal bradycardia appeared to be proportional to the duration of hypotension.

With respect to the use of spinal anes-

thesia for cesarean section, these results support the conclusion that prompt treatment of the maternal hypotension should effectively rule out this form of maternal hypotension as a cause of fetal bradycardia and presumably fetal distress. To the alert and informed anesthesiologist, this hypotension poses no great problem and can be easily corrected.

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Pressures in human umbilical vessels in utero

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ANACCOUNT of all the factors involved in the net exchange of water and the passage of intact cells across the human placental membrane must include the hydrostatic pressure gradient in the fetal placental circulation.

The umbilical vessel pressures of fetal lambs have been studied extensively; however, Haselhorst¹ is the only investigator to have made such observations on the human fetus in utero at the time of cesarean section. In 1929 he made three observations of umbilical vein pressures which ranged from 22 to 34 mm. Hg with a mean of 26 mm. Hg. He made a single observation of mean umbilical artery pressure which was 68 mm. Hg.

Our report deals with the simultaneous recording of human umbilical artery and vein pressures with the goal of ascertaining their range and relationships.

Methods

Patients studied were those undergoing elective repeat cesarean section at term. Term-sized infants were delivered in good condition with one exception noted below. Preanesthetic medication was a short-acting oral barbiturate and parenteral atropine given one hour before operation. Anesthesia was intrathecal Pontocaine weighted with 10 per cent dextrose solution. Parenteral vasoconstrictor agents were given to avoid

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Aided by Grant No. H3675 from the National Institutes of Health, United States Public Health Service. blood pressure falls with anesthesia. The patients received oxygen by mask during the operation.

Low transverse cervical cesarean sections were performed. After the uterus was opened and the amniotic fluid slowly released, the operator sought a free loop of cord which could be brought into the incision. Then one of the arteries and the vein were punctured with 22 gauge needles. Examination of the cords after delivery showed the sites of puncture to be consistently in the middle third of the cord length.

From the needles, nondistensible nylon tubing (1 mm. inner diameter) ran to standardized Statham pressure transducers sensitive in the 5 to 75 mm. Hg range. The gauge outputs were recorded through a 2 channel Sanborn recorder. If the cord could not easily be obtained or if the recording showed obvious distortion or obstruction, the procedure was discontinued and the infant delivered promptly.

Mean pressures on each record were derived with a planimeter.

Results

From 28 cesarean sections there were 7 infants on whom simultaneous measurements of umbilical arterial and venous pressures were of at least 15 seconds' duration. Four of the infants were not clinically depressed and their recorded fetal heart rates were between 120 and 160 beats per minute. They were placed in the normal group (Table I). Mean systolic pressure was 53 mm. Hg (range 50 to 56). Mean diastolic pressure

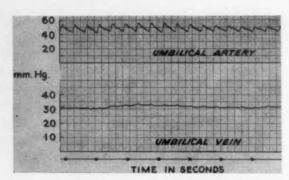


Fig. 1. Record from an infant in the normal group. Pulse 144; mean arterial pressure 48 mm. Hg; mean venous pressure 32 mm. Hg.

was 42 mm. Hg (range 36 to 46). Mean pulse pressure was 11 mm. Hg (range 10 to 14). Mean arterial pressure was 48 mm. Hg (range 44 to 52). Mean venous pressure was 24 mm. Hg (range 17 to 32). Two illustrative recordings are depicted in Figs. 1 and 2.

Table II summarizes the observations in the abnormal group in which 2 of the infants did not appear clinically depressed but had a slow fetal heart rate. In one there was a high arterial pressure and a normal venous pressure. In the other, there was a low arterial pressure and a high venous pressure.

A single observation was made on a patient for elective cesarean section at term who was delivered of a 2,460 gram infant appearing depressed at birth. This baby died 32 hours later with autopsy findings of pulmonary hyaline membrane disease. The pressure tracings are shown in Fig. 3. Pulse rate was 144 beats per minute. The systolic pressures varied from 60 to 85 mm. Hg, while diastolic pressures were 30 to 40 mm. Hg. Pulse pressure was 30 to 40 mm. Hg; mean arterial pressure was 66 mm. Hg; venous pressure was 20 mm. Hg initially and dropped to 12 at the end of the recording.

Comment

Our determinations, derived under conditions different from undisturbed intrauterine life, must be viewed cautiously. We can make no comment on the fetal vascular response to maternal spinal anesthesia and vasoconstriction. Concerning uterine incision

and amniotomy, Reynolds and Paul² noted no change in umbilical cord pressures so long as the fetal lamb remained in utero. The position of the needle in the vessel with respect to the direction of blood flow would not be expected to influence the results because Barcroft³ noted at most a variation of 2 mm. Hg. Reynolds⁴ stated that the umbilical vessels are of such size that there is relatively little change in pressure along the cord length and so the site of recording is not important.

In the normal group arterial pressures showed a small range. The observed intrauterine systolic and diastolic umbilical artery pressures are similar to those found in fetal

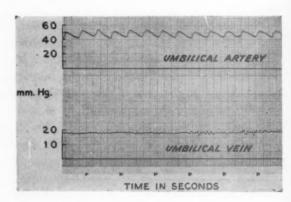


Fig. 2. Record from an infant in the normal group. Pulse 132; mean arterial pressure 48 mm. Hg; mean venous pressure 17 mm. Hg.

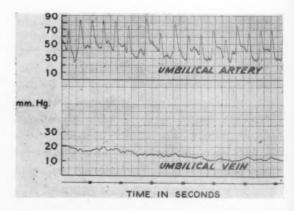


Fig. 3. Record from an infant who died of pulmonary hyaline membrane disease. Pulse 144; mean arterial pressure 66 mm. Hg; venous pressure 20 mm. Hg, dropping to 12 mm. Hg.

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Table I. Intrauterine umbilical cord pressures-normal group*

Patient	Condition of infant at birth	Fetal pulse	Systolic pressure	Diastolic pressure	Pulse pressure	Mean arterial pressure	Mean venous pressure
C. E.	Good	160	56	46	10	52	22
L. M.	Good	144	54	44	10	48	32
J. W.	Good	132	52	42	10	48	17
C. R.	Good	144	50	36	14	44	26
Range Mean		132-160	50-56	36-46	10-14	44-52 48	17-32 24

*Figures are recorded in millimeters of mercury.

Table II. Intrauterine umbilical cord pressures-abnormal group*

Patient	Condition of infant at birth	Fetal pulse	Systolic pressure	Diastolic pressure	Pulse pressure	Mean arterial pressure	Mean venous pressure
A. W.	Good	80	66	56	10	60	20
D. K.	Good	107	42	38	4	40	35
M. M.	Poort	144	60-85	30-40	30-40	66	20-12

*Figures are recorded in millimeters of mercury.

†Died 32 hours after birth of hyaline membrane disease.

lambs at term by Barcroft³ and are in the lower range of the findings in fetal lambs by Reynolds and Paul.² Haselhorst's¹ single mean umbilical artery recording of 68 mm. Hg resembles the observations in our abnormal group. His finding was upon the fetus of an eclamptic patient on whom a cesarean section was performed under ether anesthesia.

The mean value for umbilical vein pressure agrees with that recorded by Haselhorst in human subjects. It is important to note that the range is wide and resembles the variations observed in two sets of data from term fetal lambs. Barcroft³ recorded a small number of pressures between 9 and 18 mm. Hg with a mean of 14 mm. Hg. More recently Reynolds and Paul,² with a refined technique, noted a range of 20 to 35 mm. Hg on a larger number of observations with an average figure of 30 mm. Hg.

Macris and associates,⁵ in a discussion of placental hydrostatic relationships, quoted a personal communication from Prystowsky to the effect that the fetal placental capillary pressure is 45 mm. Hg. From our data on umbilical vessel pressures we may estimate the pressure in the arterial limb of fetal placental capillaries to be approximately 48

mm. Hg, while in the venous limb it approaches 24 mm. Hg. We can draw no conclusions about mean capillary pressure.

According to Starling's⁶ hypothesis, the rate of fluid passing in either direction across a capillary membrane is proportional to the difference between the hydrostatic pressure in the capillary and the sum of all pressures opposing filtration. The protein osmotic (oncotic) pressure of the plasma is most important in opposing capillary filtration of water. It has never been directly measured in human fetal blood. An approximation of it can be made by applying Scatchard's⁷ equation to data on the quantity and electrophoretic pattern of human fetal serum proteins.⁸ The figure derived for fetal protein osmotic (oncotic) pressure is 20 mm. Hg.

Comparing this with a pressure of 24 mm. Hg in the venous limb of placental capillaries, one might surmise a constant filtration of water from the fetal circulation as speculated by Reynolds.⁴ The most direct evidence against this is Naeslund's⁹ demonstration that blood specimens drawn simultaneously from the umbilical artery and vein have the same water content.

Any elevation of tissue pressure will effectively oppose capillary filtration. The

work of McKay and co-workers10 suggests that the villus has the unique property of retaining sufficient water to elevate villus pressure. They found in hydatidiform moles that water is retained on the fetal side of early trophoblast against the attraction of the higher protein osmotic pressure possessed by maternal serum. The mechanism by which the movement of water is restricted is unknown, but only two tissue elements are likely to play a role. The trophoblastic epithelium may function actively to separate two fluids of unequal osmolarity as does the human amnion. The colloid within the stroma of the villus may be similar to that within the fetus, which has a very great affinity for water as noted by Darrow.11

The observation of a premature infant who subsequently died of pulmonary hyaline membrane disease showed the most marked variations from the normal group. Significant was the elevation of systolic pressure and the falling venous pressure. These findings coincide with experiments on lambs by Reynolds and Paul. They observed that, with mild to moderate hypoxia, the fetal heart rate was variable and systolic blood pressure elevation was more consistent and of greater significance in evaluating the hypoxic fetus. They also noted that umbilical venous pressure remained relatively stable until a fall occurred with severe hypoxia.

The other two observations in an abnormal group were from infants delivered in good condition but who had heart rates below the accepted normal range. One had a low mean umbilical arterial pressure and high umbilical venous pressure, a situation which must result in a reduced placental capillary flow. The other had reversed findings which would predispose toward rapid placental capillary flow.

Summary

- 1. The mean value for umbilical arterial pressure in 4 normal term infants in utero was 48 mm. Hg with a range of 44 to 52 mm. Hg.
- 2. The mean value for umbilical venous pressure was 24 mm. Hg with a range of 17 to 32 mm. Hg.
- 3. Fetal placental capillary pressure will vary between 48 mm. Hg and 24 mm. Hg.
- 4. Villus tissue pressure may play the decisive role in controlling loss of water from the fetal placental capillaries by opposing the high hydrostatic pressure within them.
- 5. A record of umbilical vessel pressures on a premature infant who subsequently died of pulmonary hyaline membrane disease showed abnormal arterial and venous pressures compatible with intrauterine hypoxia.

We wish to thank Dr. Ernest W. Page, chairman of our department, for his encouragement and guidance; Drs. David Holman and Robert Mitchell of the Cardiovascular Research Institute for their technical advice; and the residents and nurses of the delivery suite for their cooperation.

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Rh erythroblastosis and ABO incompatibility

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The fact that ABO incompatibility protects the fetus against erythroblastosis due to Rh has long been recognized by most immunologists but has been ignored by some obstetricians. In 1950 Race and Sanger¹ summarized the work that had been done on this problem and demonstrated the curious fact that mothers of children with hemolytic disease due to Rh incompatibility were more often compatibly mated in regard to the ABO system than were unselected women (i.e., in these cases the husband could be a blood donor to his wife). Hence, the babies also tended to be compatible with their mothers in the ABO system.

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It is not difficult to calculate the probable ABO type of the infant from the types of the parents; one must merely remember the genotypes of the common types. Type O is always "OO," A is either "AO" (here A is dominant) or "AA," B is likewise either "BO" or "BB," and AB is always "AB." Then a square is drawn; for example, the mating of a Type A and Type O couple is shown in Table I (ignoring A₁ and A₂). In the first case, one half of the children are likely to be Type O, while in the second case all the children will be Type A. Calculations for all possible combinations can thus be easily performed.

To verify this assertion that ABO incompatibility protects the Rh-incompatible fetus from erythroblastosis, I investigated Rh-negative mothers from my own practice (32 cases) and from the files of two Detroit hospitals (33 cases). All babies with eryth-

roblastosis (Rh) had a positive direct Coombs test and most of them had severe cases requiring exchange transfusions. Likewise, all normal (control) babies had a negative direct Coombs test and normal hematologic findings. No case selection was permitted except that two cases of erythroblastosis in which it could not be determined whether the cause was Rh or ABO (or both) were not included and that no repeat pregnancies were counted (i.e., all pregnancies reported were from different patients). The results of this study are shown in Table II. It will be seen that the incidence of ABO incompatibility between mother and fetus is much higher in those Rh-negative mothers whose babies were normal. This difference is statistically significant (chi-square 5.15; probability close to 0.02).

There are three possible theoretical explanations for this occurrence. First, if an Rh-negative mother, for example, Type O, has Group A children, Rh-positive, her antibody-making tissues may be too fully occupied in making more anti-A to make anti-Rh: second, it may be that the A Rh+ cells enter the mother's circulation and are eliminated by her anti-A before they have time to cause Rh sensitization; lastly, the cause may be the elimination of ABO-incompatible

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	0	O		0	0
A	AO	AO	A	AO	AO
0	00	00	A	AO	AO

Table I

Table II. Relationship of erythroblastosis (Rh) and ABO incompatibility (all mothers Rh negative)*

	Fetus ABO incompatible		
	Yes	No	Total
Erythroblastosis (Rh) present	4	32	36
Erythroblastosis (Rh) not present	10	19	29
Total	14	51	65

^{*}Average parity of mothers of erythroblastotic babies was 1.9 and average parity of mothers of nonerythroblastotic babies was 4.0.

Table III. Chances of sensitization to Rh

	ABO com	ABO type of		
Husband's zygosity for Rh	Incom- patible (%)	Compatible (%)	husband unknown (%)	
Heterozygous	1	3	2	
Homozygous	4-5	11	9	
Zygosity unknown	2-3	7-8	5	

children, irrespective of Rh groups. Levine¹ found fewer A children when the mother was O and the father A than when the mother was A and the father O. Fisher¹ has suggested that this elimination of ABO-in-

compatible fetuses early in pregnancy would reduce the amount of anti-Rh production. I favor the second explanation which seems to agree with clinical experience.

However, regardless of the actual cause of this phenomenon, it may be used by the obstetrician as a guide in prognosis both in the present and in future pregnancies. In their recent book, Allen and Diamond² tabulated the chances of eventual sensitization to Rh by pregnancy alone in the Rh-negative wives of Rh-positive men (Table III). In their opinion, ABO compatibility doubles the chance of the occurrence of Rh sensitization.

Summary

- 1. An old theory that ABO incompatibility protects (or is associated with) the fetus from Rh sensitization is re-emphasized.
- 2. Data from my practice and from two hospitals are presented which support this theory.
- 3. Possible causes for this occurrence are discussed and its prognostic importance emphasized. Besides the Rh-positive husband's zygosity and the previous obstetric history, the ABO compatibility of the husband and wife (or mother and fetus) should be considered.

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Microsomia fetalis

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MICROSOMIA fetalis characterizes the undersized and underweight infant born at term. Since his weight ranges from 1,800 to 2,500 grams, or $3\frac{1}{2}$ to $5\frac{1}{2}$ pounds, instead of the usual weight of 3,400 grams, or $7\frac{1}{2}$ pounds, he is considered to be premature. A considerable literature has accumulated on the macrosomatic, or excessive-sized infant weighing over 4,000 grams, or 83/4 pounds, according to Ouinto and associates. Yet little has been said about its counterpart, the microsomatic child.

My experience with 9 cases, as well as several inquiries from colleagues who have delivered small babies at term, prompted the preparation of this report.

Incidence

I have observed 9 microsomatic infants in approximately 700 private obstetrical patients, or 1.3 per cent. The incidence of prematurity, based on viable infants weighing less than 2,500 grams, is between 5 and 6 per cent. Therefore, it would seem that about one fifth of the supposed premature infants were microsomatic instead.

Maternal factors

All of the mothers have been white, American born, usually of English, Scotch-Irish, and German descent. They have been of average size and weight and in good health. Some were primiparas and others were multiparas. Several had been treated for sterility. Others had a history of a previous still-birth. Their pregnancies were usually un-

eventful without anemia or toxemia. The salient feature was the failure of the uterus to increase in size during the last trimester of pregnancy. Sometimes the labor was complicated by fetal distress. Delivery occurred at term or slightly beyond. The following is a report of a recent case.

Case 1. Mrs. J. H., age 30 years, white, gravida ii, para i, Rh-negative, the wife of a physician who was Rh-positive, had one previous delivery of a baby weighing 7 pounds, 5 ounces. The present pregnancy was uneventful excepting for a failure of the uterus to increase in size during the last 2 months, the measurement remaining stationary at 27 cm. without descent of the head. The pregnancy went one week past term. For these reasons, even though no antibodies had developed to the Rh factor, and because microsomia fetalis was suspected from past experience, labor was induced by artificial rupture of the membranes, the cervix being favorable and the uterus irritable. Spontaneous delivery occurred after a short labor of 2 hours and 20 minutes. The baby weighed 5 pounds, 4 ounces, or 2,380 grams. It was Rh-positive, Coombs negative. There was marked spiraling of the cord which could not be stripped of blood. The placenta weighed 450 grams.

The weight of the infant declined to 2,210 grams on the fourth day of life after which it increased gradually so that, by the sixteenth day, it was back to its birth weight. At the end of 4 weeks it weighed 2,830 grams. By the fourth month it weighed 15 pounds, and in 9 months the weight had reached 21 pounds. This performance was even better than an average 7 pound infant who doubles his weight in 5 months.

Fetal factors

The infant is undersized and underweight at birth. His weight ranges from 1,800 to

From the Departments of Obstetrics and Gynecology, College of Physicians and Surgeons, Columbia University, and St. Luke's Hospital, Women's Hospital Division. 2,500 grams or from $3\frac{1}{2}$ to $5\frac{1}{2}$ pounds. He has a stunted appearance, with a wrinkled, dry skin without much subcutaneous fat. The nails are long. Except for the difference in size and weight, he resembles the postmature infant of Clifford² and the dysmature child of Sjöstedt and associates.³

The placenta is usually smaller in circumference and weighs less than the usual 600 grams. Most weigh between 400 and 450 grams. They are more fibrous and have calcium deposits on the maternal surface. The dependence of the size and weight of the newborn child on the size and weight of the placenta has been well established by Knaus. Commenting on this article, Greenhill mentioned having delivered a 3 pound, 6 ounce infant at full term with a fibrosed placenta and said, the small size of the baby was due to the insufficient amount of placental tissue to nourish it."

The umbilical cords are usually quite thin, owing to a reduction in Wharton's jelly. They have three vessels which show varying degrees of spiraling, which in the case reported above was so marked that one could not strip the cord of blood into the infant. The importance of the cord in serving as a good "life line" should be stressed. While the size of the placenta governs the size of the baby and vice versa, one must not overlook the role of the cord in these relationships. It is like the stem of a garden flower; when faulty, the flower becomes stunted or dies, as does the root system. While microsomia fetalis may be caused by a small fibrosed placenta, it can also be produced by excessive spiraling of the cord. However, not all infants with spiraled cords are premature by weight. Some range between 2,500 and 3,000 grams as in Case 2.

The degree of normal spiraling of the blood vessels in the umbilical cord will vary from almost a straight line to a spiral staircase. It will also vary according to the duration of pregnancy and whether the cord is short and thick or long and thin. Excessive spiraling is a somewhat arbitrary term but it is used in this article to designate more

than 8 turns of the umbilical vein per 10 cm. of cord. Under such circumstances stripping of the cord may be difficult or impossible, which is probably physiologically more important than the anatomical spiraling. I have observed excessive spiraling of the cord in successive pregnancies in the same patient on several occasions.

Case 2. This patient, age 23, white, the daughter of an obstetrician, had experienced one fetal death in utero at term, followed by one miscarriage. Because of extreme apprehension and anxiety she had been promised delivery 2 to 3 days before term in the next pregnancy. This pregnancy was uneventful and labor was induced 3 days before the due date with an intravenous Pitocin drip. Mild contractions ensued which were sufficient to produce fetal distress; this disappeared when the Pitocin drip was discontinued. Fearing placental deficiency as discussed by Randall⁶ we deemed it best to perform a cesarean section. The baby weighed 2,890 grams, or 6 pounds 6 oz., which is somewhat less than average. The placenta was of normal weight, namely, 650 grams. The cord was 45 cm. long and exhibited excessive spiraling of the vessels. The patient's father believed that there had been a similar cord condition at the time of the stillbirth.

Neonatal period

These infants are often sent to the premature unit on the basis of their weight. They take to the bottle with gusto and begin to gain almost at once. Thereafter, growth and development is rapid, as illustrated in Case 1.

Perinatal mortality

There were no fetal deaths in these 9 cases. Evidently, a much larger series of cases is required to establish the relationship of microsomia fetalis to fetal mortality. Evidently, most of them have been classified under "prematurity" and thereby excessive spiraling of the cord as the causative factor has been ignored. Stunted growth of embryos and fetuses that die in utero, before viability, of cord complications including spiraling of the cord have been described elsewhere.

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Summary

- 1. Microsomia fetalis characterizes the undersized and underweight infants born at term who weigh between 1,800 and 2,500 grams, $3\frac{1}{2}$ to $5\frac{1}{2}$ pounds.
- 2. Nine cases have been observed in 700 private cases for an incidence of 1.3 per cent.
- 3. About one fifth of the infants considered premature by weight are probably examples of microsomia fetalis.
- 4. While microsomia fetalis may be associated with small placentas and placental deficiency, the striking feature in these cases was an excessive spiraling of the cord.
- 5. Excessive spiraling of the cord may be anticipated when fetal distress occurs in spontaneous or induced labors.
- 6. Excessive spiraling of the cord may also be found in infants considered full term by weight, but smaller than average.

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The acardiac monster

A review of the world literature and presentation of 2 cases

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THE recent occurrence of 2 cases of acardiac monsters on the Obstetrical Service of Harlem Hospital prompted the writing of this paper. Since the first 2 reported cases of acardia in 15331 and 1539,2 and a review of cases in 1902,3 there has been no cumulation of the cases in the world literature. The authors have attempted as carefully as possible to collect these cases from the English and foreign languages, to bring to date the total number of reported cases and to review and clarify the classification of these monsters.

Schatz⁴ classified hemiacardius (imperfectly formed heart) and holoacardius (absence of heart) as major groups. Das3 more clearly subdivided the holoacardiacs into acephalus, amorphus, anceps, and acormus. Although Simmonds & Gowen⁹⁸ added another subgroup, i.e., myelacephalus, we have placed this along with the so-called fetus amorphus anideus within the amorphus group for reasons to be mentioned. These monsters have been termed chorioangiopagus parasiticus by Schwalbe,5 since this defines the entire dependency of the monster on the blood supply of its normal and identical

The following are 2 cases of acardiac monsters which will be added to the cases in the world literature:

Case 1. M. B. (No. 59-1830), a 37-year-old Negro woman, gravida i, para 0, was admitted

to the hospital from the prenatal clinic at 30 weeks of gestation because of mild pre-eclampsia. The prenatal course had otherwise been normal. Previous medical and surgical histories were noncontributory. Gynecologic history showed regular menses with no inflammatory disease. The patient had been married 13 years and used no contraceptives. Her husband was 42 years old and healthy. After 7 days of hospitalization, pre-eclampsia subsided and she was discharged. She was readmitted 3 weeks later because of premature rupture of membranes, but she was not in labor. The uterus was 34 to 36 weeks size; fetal heart sounds were good. Vaginal examination revealed a posterior cervix, with the os closed and leakage of amniotic fluid stained with meconium. X-ray examination of the abdomen revealed a premature fetus with breech presenta-

After 6 hours of observation, and on the basis of 13 years of infertility in an elderly primigravida, premature rupture of membranes, an unfavorable cervix, and breech presentation, a cesarean section was performed. Through a low cervical transverse incision, a premature living male child was delivered from a left sacroanterior position. Birth weight was 2 pounds, 10 ounces (1,181 grams). During an attempt to deliver the placenta, a second set of membranes was discovered and ruptured. After some difficulty, an acardiac monster was delivered by grasping a slippery short "extremity." Its atrophic umbilical cord tore at delivery but arose from an umbilical hernia (Fig. 1). The placenta was delivered intact, and the uterus and abdomen closed. The patient recovered and was discharged on the eighth postoperative day. The premature infant lived and was discharged well from the nursery at age 2 months, weighing 5 pounds, 1 ounce.

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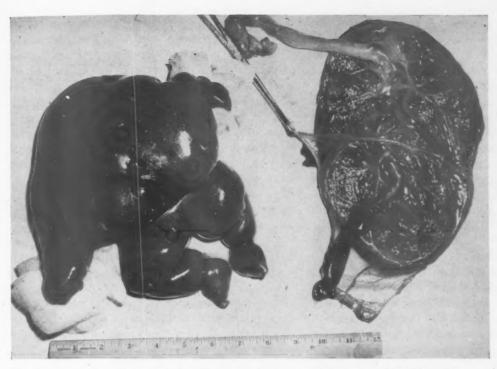


Fig. 1. Case 1. Acardius acephalus. Note the glossy and edematous surface. Note the single placenta, the double amnion, and the abnormal cord, which is the same color as the monster.

Pathology report. The specimen was that of a stillborn male monster weighing 3 pounds, 14 ounces (1,744 grams), consisting of a liver-like reddish mass of tissue, soft and boggy, measuring 25 by 17 by 10 cm. The lower extremities were more or less distinct with 2 toes each. The upper extremities showed phocomelia. There was no head, the top of the monster coming to a blunted end. The ventral surface was identified by a penis 2 cm. long with no testicles. Seven centimeters above this there was a soft mass 5 cm. in diameter, an omphalocele, from which the umbilical cord had arisen. An incision on the ventral surface revealed remnants of gastrointestinal tract in the form of a tubular organ about 10 cm. in length beginning in a blind end and terminating in an imperforate anus. This appeared to be colon. No other organ could be identified. There were no cardiac or pleural structures. There was a cartilaginous, bony skeleton and a spinal column (Fig. 2). In the upper pole of the monster, about 25 c.c. of clear yellow fluid was present (presumably cerebrospinal fluid) in a nondescript cavity about 2 cm. in diameter. The omphalocele contained a loop of colon and yellow fluid. Its wall was thin and of the same consistency as the rest of the monster.



Fig. 2. Case 1. X-ray of acardius acephalus. Whitish area at cephalic end is artefact. Note the relatively well-formed rib, pelvic, and long bones. No cranial bones could be seen.

Microscopy findings. The only organ that could be identified with certainty was the intestine. This was identified as colon, markedly distended, with resulting partial atrophy of the mucosa. A considerable part of the epithelium, which was somewhat degenerated, partially filled the lumen of the gut. The mesentery contained arteries and veins which were largely devoid of red cells although they had wide lumina. Nerve trunks were also visible in the mesentery.

A piece of tissue from the surface of the body had no epithelial covering and consisted of congested, edematous, very loose mesenchyma, with hemorrhages close to the surface. Areas of degenerated tissue with calcifications were also seen. Sections through the various parts of the fetal tissue consisted of loose fibrillar tissue which took a pale eosinophilic stain and which in places was condensed into denser bundles, taking a deeper stain. The nuclear elements in some places were elongated, resembling mesenchymal nuclei (Fig. 3), and others were arranged in irregular clusters and appeared predominantly round. In several places pieces of well-formed cartilage were encountered. In others, there were small spicules of irregularly formed bone. Scattered small islands of squamous epithelium were seen, and, in their proximity, tubular glands with double rows of nuclei resembling oversized sweat glands were found. The fibrillar tissue, especially from what was called the "top" of the monster, showed areas of rarefaction with areas of empty lacunae. A number of tiny blood vessels were preserved and formed a loose meshwork within the lacunae. In a few places, there were plump-like collections of calcific material in areas of partial softening of the tissue. Brain tissue elements were identifiable. No liver or lymphoid tissue could be identified in numerous blocks of tissue.

The placenta was one of a twin (identical) pregnancy, with one chorion, two amnions, and a single placental surface. The umbilical cord of the monster was reddish and atrophic and contained two umbilical arteries and one vein.

Final diagnosis. Acardiacus acephalus.

Case 2. O. P. (No. 54-17852), a 25-year-old Negro woman, gravida i, para 0, was admitted to the hospital in active term labor at 42 weeks gestation. Past medical and surgical histories were negative. Gynecologic history revealed normal menses and no history of inflammatory disease. The prenatal course was uneventful. She was married one year. Her husband was 27 years old and healthy. Pertinent physical findings revealed a term-sized uterus, good fetal heart sounds, and a vertex presentation. Labor progressed slowly and after 37 hours the patient

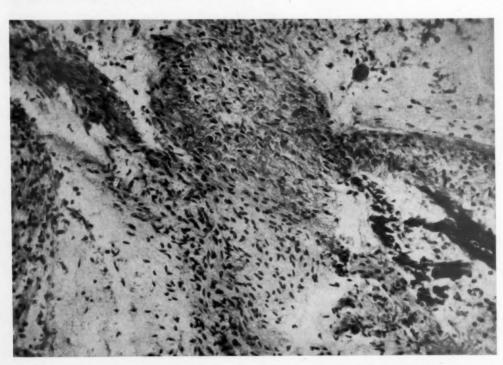


Fig. 3. Case 1. Section through one area of the body surface showing mesenchymallike nuclei. Note area of nonspecific calcium deposition. (×50; reduced 1/4.)

was delivered of a normal 6 pound, 14 ounce female child. Along with the delivery of the placenta, a globular mass of tissue was passed. The patient had an uneventful postpartum course and was discharged on the sixth day.

Pathology report. "This specimen of an undeveloped human twin . . . has proved upon dissection to be a case of fetus amorphus anideus. It consists of a featureless mass, 6.4 by 5 by 3.8 cm., composed of adipose, fibrous, and muscle tissue surrounding an osseous core and enclosed in a hair-bearing covering of skin (Fig. 4). The anomaly shows remarkably well-developed vascular connections with the placenta. There is, however, no fetal heart, the vessels ramifying within the mass in a haphazard plexus. Of particular interest are the well-developed umbilical vessels (one artery, one vein) which ramify among the osseous fragments."* The placenta was single, with one amnion and one chorion, apparently that of a monoamniotic, monozygotic twin pregnancy.

Incidence

We are concerned solely with the holo-acardia group of "heartless" monsters. They have been reported 149 times in the world literature. It has been calculated that they occur once in 34,600 deliveries.⁶ This is based on their occurrence in about 1 per cent of monozygotic twins, which, according to Guttmacher, ¹⁰⁷ account for 25 per cent of all twin births. Further, there have been reported 7 acardiacs in as many triplet deliveries. ^{11, 14, 50, 64, 71, 98, 106}

In the past 28 years at Harlem Hospital, we have had 1,055 sets of twins in 84,000 deliveries (1 in 79). Calculating that one fourth of twins are identical, our incidence of acardia is three fourths of 1 per cent—an agreeable comparison in view of the rarity of the condition.

Classification

Depending on the stage of development or lack of development of the monster, the following categories are found:

*Described, studied, and presented by Dr. Elizabeth M. Ramsey, Department of Embryology, Carnegie Institution of Washington, to the Sixty-ninth Annual Session of the American Association of Anatomists at Marquette University School of Medicine, Milwaukee, Wisconsin, April, 1956.

- 1. Acardius anceps. This is the most highly developed form. It has been reported 12 times⁶⁻¹³ in the literature (4 cases being reported by Das³). There usually is present a partly developed head with remnants of cranial bones and brain tissue. The face is imperfect with various clefts in place of ears, eyes, or mouth. The body and extremities are developed. There may or may not be a definite thoracic cavity although a formed heart is never found.
- 2. Acardius acephalus. Ninety-three cases of this variety (of which 38 were described by Das), the most common of the acardiacs. have been reported.14-67 They are headless and lack thoracic organs. If a diaphragm is present, it is rudimentary. The ribs are usually developed but thoracic vertebrae are either lacking or reduced in number. The abdomen might contain remnants of liver, spleen, kidney, or intestine. Underdeveloped gonads are occasionally found. The anus may be imperforate. Pelvic bones and the lower extremities are well developed, but the upper extremities may or may not be present. We have presented one such case (Case 1).
- 3. Acardius acormus. This is the rarest form of acardia. There have been 7 such cases reported⁶⁸⁻⁷¹ (3 by Das). The monster is a head without a body. The only semblance of a body (if present) is a shriveled mass of tissue. The head is attached to the placenta either directly or via an umbilical cord ending in its cervical region.
- 4. Acardius amorphus. This least developed monster is not recognizable as a human form. Having been reported 37 times^{44, 58, 72-103} (2 cases by Das), it may have the appearance of a "blob" or ball of skin with or without hair. In this instance it is called "fetus amorphus anideus." Its interior contains bone, cartilage, fat, fibrous and muscular tissue, and blood vessels. It differs from a dermoid cyst in that it is attached to an umbilical cord, and occasionally a well-formed structure, e.g., a femur, may be found within it. The acardius myelacephalus is club-shaped and x-ray examination may reveal a skeletal frame with

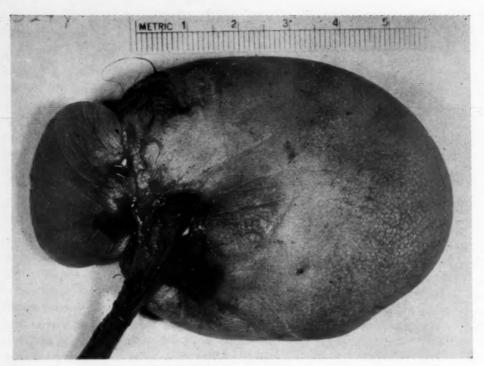


Fig. 4. Case 2. Fetus amorphus anideus acardiacus. Note the umbilical cord attached to lower pole, the wrinkled skin, and the hair at one end. On cut section the mass was of the same consistency throughout.

one or more extremities, sometimes fused. Minimally developed visceral organs may be encountered in the abdomen. Since this type has no gross human form we have included it in the amorphus group.

Umbilical cord pathology

In the above groups of monsters the umbilical cord may vary from short to normal in length and may appear atrophied, edematous, and darkened in color. It may contain either two arteries and one vein (as in Case 1) or one artery and one vein (as in Case 2). The latter condition may be due to poor completion of structural development in the embryonic period. It is interesting to note that it occurs in the least developed form of acardia, the acardius amorphus. The monsters may rarely be monoamniotic.

Etiology

It is an accepted theory that the "life" or sustenance of the monster is completely parasitic; it receives its blood supply directly

from the umbilical arteries of the normal fetus. Therefore, the only pressure gradient is away from the normal twin's heart, and blood rushing from the normal fetus to the placenta (and then to the circulation of the monster) is poor in oxygen and nutriments and gives relative stagnant anoxia to the parasitic monster.

As to why there is a direct intercommunication between the two arterial systems is conjecture. Claudius¹⁰⁴ pointed out that, of the identical twins, the allantoic stalk of one contacts the chorion (which enters into the formation of the placenta) much before that of the other. Thereby, the umbilical vessels are developed earlier in the first twin. Later, because the second twin finds only a limited placental surface or perhaps none at all, its umbilical vessels become attached to those of the first. As the placenta grows, the vessels elongate and serve both growing embryos with circulating blood with the blood pressure arising in the first twin.

' Embryologically speaking, it would seem

that the heart does not atrophy as some authors postulate⁸³ but that the sparseness of building materials for the second fetus causes failure of further development. This would explain the primitive tubular heart found in some acardiac monsters. As for the development of certain particulate tissues in acardius amorphus, this can be explained by the fact that anlage, specific developmental cellular areas, may proceed to form portions of intestine or a length of femur. The fetus amorphus anideus fails completely in development because of its pitifully poor blood supply.

Clinical aspects

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The patient may be of any age, of any parity, and with or without a history of repeated abortions. She need not have a history of disease early in the prenatal course. Hydramnios occurs commonly. The patient may undergo premature labor or may carry to term. The labor is not unusual, with the normal twin being delivered first. The anomalous twin, not usually diagnosed prior to delivery, may present before or after the placenta. If the monster has any shape of human form, it will usually be delivered by footling breech, since the poorly dilating, soft, boggy, "cephalic" end does not present. Suffice it to say that when one of these monsters is delivered diagnosis is relatively obvious. Extreme caution, however, as with any monster, must be adhered to during delivery. Rupture of the uterus, dystocia because of large size, and postpartum hemorrhage have been seen with this condition.

Although the occurrence of most monsters increases the chances of its happening again

in that patient by 25 times, there has never been reported a case of repeated acardia. This would lead one to believe that acardia is a freakish accident rather than the theoretically explainable occurrence of, for example, repeated anencephalia.¹⁰⁵

Summary

- 1. Concerning holoacardia, a rare group of monsters, we have reported 2 cases, making a total of 151 cases to date in the literature.
- 2. Photographs and x-ray pictures in this article are typical for the conditions reported.
- 3. We have classified the groups and subgroups of holoacardia as (1) acardius anceps, (2) acardius acephalus, (3) acardius acormus, and (4) acardius amorphus.
- 4. It is interesting to note that the immaturity of the monster is directly proportional to the complete development of the umbilical cord.
- 5. The etiology and clinical picture of this condition has been presented following a complete study of the world literature.

We wish to express our gratitude to Dr. Vera Dolgopol, Director of Department of Pathology, Harlem Hospital, for the pathologic description of the first case and to Mr. E. Entin, photographer, for the pictures used. Further, we are indebted to Dr. Evan Gordon, who delivered the patient in Case 2, and to Dr. Elizabeth M. Ramsey, Department of Embryology, Carnegie Institution of Washington, for her study, description, and presentation of this case in 1956. We especially wish to thank our Director of Service, Dr. A. C. Posner, for his invaluable aid in the preparation and selection of material in this report.

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Abdominal lithopedion retained for 13 years

Case report with review

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AMONG the numerous individual reports1-48 and several brief reviews of retained abdominal pregnancy there are many cases of compound pregnancy where normal gestation and delivery have occurred during the retention of a lithopedion. To our knowledge, however, there is only a single case reported38 where an abdominal pregnancy was observed at laparotomy, unrecognized as such, and then later removed in the form of a lithopedion. The case herein reported is of unusual interest because of the three following features: (1) observation of the abdominal pregnancy by others in 1944 during a laparotomy, when the nature of the findings was not recognized; (2) delivery of a normal child two years later; and (3) final removal of a well-preserved lithopedion in 1957.

The patient was a 51-year-old Negro housewife, first seen by us June 11, 1957, because of an attack of diarrhea and abdominal pain thought to be due to epidemic viral gastroenteritis. This patient had been married at the age of 18 and had 3 living children, ages 34, 31, and 11, born in 1923, 1926, and 1946. In the summer of 1943 the patient had experienced lower abdomir.al and epigastric pain and in the fall of 1943 was discovered by another physician to have an abdominal mass, considered to be a fibroid uterus. On Jan. 13, 1944, the patient underwent abdominal laparotomy. Because of its pertinence to the present illness, the surgeon's

operative note is quoted in full as follows: "Midline incision opened abdomen. Free bloody fluid was present. There was a huge mass lying in the left lower abdomen, probably a fibroid, but omentum, highly vascular, was adherent to this mass. In the right pelvis is another mass, undoubtedly a malignant ovary. Lying in the upper abdomen, retroperitoneally, is a third mass, the size of my fist, undoubtedly a metastatic growth. No attempt was made to remove any material from the abdomen due to the obvious high vascularity of the tissues. Postoperative diagnosis-cancer, metastatic throughout the abdomen." Inspection of the hospital record at this time reveals that no x-rays were taken, and no tissue was removed for pathological examination. The patient was informed that she had "inoperable malignancy."

Two years later in 1946 the patient was delivered of a normal baby who was living in 1957 at age 11. The events surrounding this delivery are of interest. Her attending physician at this time persistently blamed the patient's predelivery symptoms on the intra-abdominal malignancy. This last child was born in the patient's home, much to the surprise of mother and attending physician.

A physical examination in June, 1957, revealed an obese, middle-aged Negro woman in apparently excellent health. Blood pressure was 176/106. There was no abdominal tenderness, but there was a very hard nodular mass, extending up from the pelvis almost to the umbilicus, considered to be uterus. On pelvic examination it was not certain that the uterus was definitely connected with this mass, but it was thought that it probably was. There were two small endocervical polyps. Otherwise, com-

From the Davis Clinic and the Davis Medical Foundation.

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plete examination was entirely within normal limits.

Urinalysis showed numerous trichomonas organisms and white blood cells in a voided specimen, a specific gravity of 1.012, but no albumin or sugar. The hemoglobin level was 13.15 Gm. per cent, and the hematocrit 42 vol. per cent. The white blood count was 8,000 with 65 per cent polymorphonuclear leukocytes and 37 per cent lymphocytes. The Mazzini test was negative. Roentgenogram of the chest showed the cardiac silhouette within normal limits in size. There were a few calcific deposits in the right hilar region in the right lower lobe, but the lung fields were otherwise clear. Cholecystogram showed a normal gall bladder filled with dye in good concentration without evidence of calculi. An upper gastrointestinal series was normal, except for some irritability of the duodenal bulb. On these films the patient's abdominal mass was demonstrated to contain a fetal skeleton, estimated by its size and development to be of about 6 months' gestation (Fig. 1).

This surprise finding prompted the securing of a more obstetrically oriented history, which indicated that the patient's last normal menstrual period was 21/2 months preceding this observation, rather than the expected 6 months. At no time during the next few weeks was fetal movement or fetal heartbeat recognized. Repeat flat films of the abdomen then clearly showed extensive calcification in the soft tissues of the fetus, and a preoperative diagnosis of lithopedion was

On Oct. 3, 1957, an elective laparotomy was performed. "A calcified fetus was found lying free in the abdomen, except for attachments of omentum to the ventral surface of the fetus. There was a loop of small bowel attached to the ventral surface. These structures were freed by sharp dissection. The calcified fetus of about six months' gestation was then removed and the pelvis was explored. Adnexal regions were entirely normal. Both tubes and ovaries were normal. The uterus was anterior and normal in size." There was no evidence of a residual placenta and no evidence of the new growth described in the operative note of 1944. The patient has made an uneventful recovery from this procedure and is relieved of chronic abdominal distress, indigestion, and diarrhea which had plagued her in the guise of gallbladder attacks for many years. She is living and well 11/2 years after removal of the lithopedion.

The fetus removed was a remarkably well-preserved "stone child" (Figs. 2 and 3), measuring 19.5 by 9.5 by 8.5 cm. and weighing 21/2 pounds. The facial features had been moulded into an unrecognizable mask, but fingers and toes were clearly identified, fused to the torso and folded extremities as though the whole specimen were an incomplete piece of sculpture. Hair was present over the occiput and anterior fontanelle. There was no trace of placenta, membranes, or umbilical cord.

Comment

Not only the medical problems but also the sociological and psychological problems of retained extrauterine pregnancy have been used at least once in literature as the nucleus of a fascinating plot in fiction. Samuel Hopkins Adams,46 in a novel concerning medical practice along the Erie Canal during the early nineteenth century, describes the downfall of a young frontier doctor who makes a diagnosis of pregnancy in the unmarried daughter of the town's leading citizen, only to have the young lady



Fig. 1. Preoperative flat film of the abdomen showing soft tissue calcification in the intraabdominal fetus.

fail to deliver at the predicted time. The physician's professional and social ruin is reversed only when an illegal midnight graveyard autopsy vindicates his original medical judgment. This piece of fiction is based on an actual case of lithopedion reported only in lay literature, in the New Yorker Magazine, Dec. 10, 1938.⁴⁷

A recent case report of lithopedion in American medical literature⁴⁰ was deemed newsworthy enough to be quoted in the medicine section of Time Magazine. The authors of this case report claim that their lithopedion represents the two hundred fifty-nineth reported case in medical literature. Although it serves to emphasize the rarity of this condition, it is doubtful whether this figure is entirely accurate. A recent report in the German literature41 claims to be the two hundred fiftieth reported case In addition several cases38, 44, 45, 47 have been found which are not included in the bibliography of either of these recent case reports. The exact accounting of the reported cases of lithopedion in the world literature is also confused by the fact that



Fig. 2. Lithopedion photographed immediately after removal from its mother's abdomen.

many reviews include cases of retained abdominal pregnancy which have autolysed into fragments of fetal skeleton and other degenerated relics which could hardly be termed true lithopedia. Whether a retained abdominal fetus remains for years as a recognizable calcified "stone child" or degenerates in time into a small encysted sac of fetal bones is an accident of nature, and both result from the same original obstetrical anomaly. There are two well-documented cases8, 41 where nearly full-term skeletons of intra-abdominal pregnancies have been observed by serial roentgenograms to degenerate in time into much smaller masses of calcified fetal parts, which would hardly satisfy the criteria of a true lithopedion.

When an intra-abdominal pregnancy, either primary or secondary, is retained without surgical intervention, a number of quite different solutions to this problem have been demonstrated by nature. One of the earliest reviewers of this phenomenon, Kuechenmeister,1 divided various forms of retained abdominal pregnancy into three classes: (1) lithokelyphos, or calcified membranes with degeneration of the fetus within them, (2) true lithopedion, or a calcified fetus without calcification of the membranes, and (3) lithokelyphopedion, or calcification of both the fetus and membranes. This nineteenth century classification has been preserved by repeated quotation throughout the numerous case reports, but it seems less meaningful in view of modern pathological concepts than a classification proposed by D'Aunoy and King in 1922.5 These authors propose a classification of retained abdominal pregnancies into four possible categories: (1) skeletonization, or the retention of a collection of fetal bones with absorption of fetal soft parts, (2) adipocere, or replacement of the soft parts by soaps and fats, (3) suppuration, or abscess formation due to infection with destruction of the fetal tissues, and (4) true lithopedion, or sterile calcification of the fetus. Many of the reported cases of "lithopedion", 9, 10, 21, 22, 25 have actually been cases of skeletonization or collections of fetal bone fragments discovered

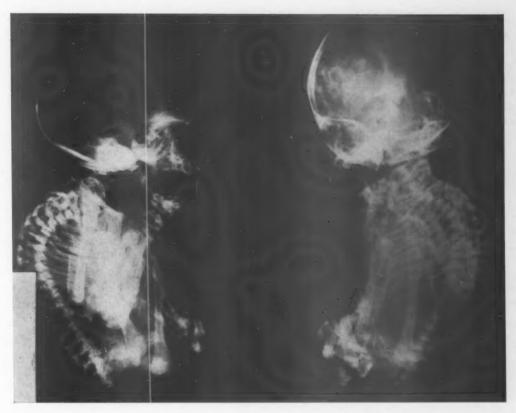


Fig. 3. Roentgenogram of the removed lithopedion showing the excellent preservation of the fetal skeleton in spite of 13 years' incarceration.

encysted in the pelvis at laparotomy or autopsy.

The retention of an abdominal pregnancy indefinitely until operation or autopsy reveals its presence is only one of the numerous possible terminations of extrauterine pregnancies. Gould and Pyle's Anomalies and Curiosities of Medicine,48 published in 1901, lists an extensive bibliography concerning the natural terminations of abdominal pregnancies. These include the extrusion of fetal parts through the abdominal wall48-50 as well as the delivery of fetal bones and even intact lithopedia through every body orifice. Gould and Pyle report a case where the delivery of a whole fetus by mouth was performed on several occasions in the same patient, and even on one of these occasions the delivery of both fetus and placenta by this oral route. There are numerous incidences of the delivery of fetal parts, particularly fetal bones, by rectum48, 50, 51 and several cases of intestinal obstruction⁵² from the impaction of fetal parts within the lumen of the gut, as well as from adhesions produced by degenerating intra-abdominal pregnancies.⁵⁰ Pieces of calcified fetus have been passed in the urine^{48, 50, 53} and at one autopsy an intact fetus was found neatly contained within the urinary bladder.⁴⁸ There are many reports of the delivery of fetal parts through the vagina from abscesses formed in the pouch of Douglas⁴⁸ and others through the anterior vaginal wall^{48, 54-56} where the abdominal pregnancies were located between the bladder and uterus.

There are several incidences reported^{9, 31} of compound intrauterine and extrauterine pregnancies with lithopedion formation from the extrauterine pregnancy. There are innumerable cases where women carrying lithopedia or retained fetal parts have had concomitant normal pregnancies and deliveries. There is even a case³⁶ of an intrauterine

lithopedion being delivered wrapped around the neck of a living twin. In view of the modern debate as to whether the placenta should be left in situ when an abdominal pregnancy is delivered, it is interesting to note what is recorded about the preservation of the placenta in cases of retained abdominal pregnancy.^{3, 18, 21, 28, 34} Many case reports do not adequately describe whether a placental remnant is present or not, but where such mention is specifically made the cases are about equally divided between those where no trace of placenta is found and those where a definite placental remnant, usually also calcified, is identified.

The observation of a lithopedion in the second half of the twentieth century implies either that the patient involved has had no medical attention whatever, or that some rather serious mistakes in medical judgment have been made. It is of interest that most of the modern case reports of lithopedion originate from parts of the world where medical care does not approach the standard maintained in Western countries. Obviously, a retained abdominal pregnancy should be recognized eventually in any modern obstetrical practice. The case of retained abdominal pregnancy herein reported is of special interest because it was probably observed at laparotomy 13 years before it was removed. At this time the nature of the findings were not recognized, and, in fact, it was assumed to be a case of an inoperable metastatic cancer. This error in medical judgment stemmed from two basic mistakes. These were the failure to obtain a flat film of the abdomen preoperatively, and failure to biopsy the tissue observed at laparotomy. Laparotomy for large abdominal masses should always be preceded by a minimum of a flat film of the abdomen.

A case very similar to the one reported here has been recorded by Gilman, Schwartz,

Stephenson, and Settle in 1954.38 Their patient, an Eskimo woman, had a laparotomy in June, 1949, when "the entire left side of the abdomen and the pelvis was filled with an irregular mass. . . . A diagnosis of a retroperitoneal tumor was made. No attempt was made to remove or biopsy the tumor." In 1953 a flat film of the abdomen revealed fetal parts. This patient was operated upon a second time and "A fetus about the size of a full-term pregnancy was found, surrounded , completely by thickened membranes. . . . No structure which could be interpreted as a placenta could be found. . . . A total hysterectomy and bilateral salpingo-oophorectomy was performed, removing the fetus and genital organs en bloc. . . . Within the lumen of the mass the fetus was partially calcified and mummified with some autolysis of the cutaneous and subcutaneous tissues. The fetus weighed 3 pounds, 1 ounce and showed no obvious major anomalies."

Summary

1. A case is reported of abdominal pregnancy retained for 13 years, terminated by the removal of a well-preserved $2\frac{1}{2}$ pound lithopedion in 1957. The patient had had a laparotomy in 1944 when a massive intraabdominal "malignancy" was described. The error in diagnosis made at this time was possible because of the failure to obtain a preoperative flat film of the abdomen and the failure to biopsy the abnormal tissue observed at the time of operation. Two years later in 1946 while carrying the retained abdominal pregnancy, the patient was delivered of a child, who is now living and well.

2. A review of the literature on this subject emphasizes the fact that lithopedion formation is only one of the numerous possible terminations of retained abdominal pregnancy.

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Preparation and use of antisera to human chorionic gonadotrophin

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H U M A N chorionic gonadotrophin (HCG), a macromolecular protein hormone, would be expected to act antigenically in a heterologous species. Crude anti-HCG sera have been developed previously which demonstrate a precipitin reaction and a neutralization effect on biological activity. The impurity of earlier hormone preparations made contaminating antibodies inevitable. The impurities, which are strongly antigenic, may also inhibit the formation of antigonadotrophin antibodies.

The improvement in methods of purification of protein hormones and the use of Freund's adjuvant permitted the development of potent antisera against growth hormone.^{4, 5} Likewise, a highly purified human chorionic gonadotrophin preparation has made possible a specific antiserum which could be used successfully for the detection of HCG in biological fluids. Preliminary studies indicate that the test compares favorably with the Friedman assay in terms of reliability and sensitivity.

Methods

1. Hormone. The highest specific activity reported for a human chorionic gonadotrophin preparation is 12,000 I.U. per milligram.⁶ Previous purifications achieved no greater then 8,500 I.U. per milligram.⁷ The

From the Department of Obstetrics and Gynecology, University of California School of Medicine.

*National Institutes of Health Post-Doctoral Research Fellow in Pediatrics and Obstetrics supported by NIH Grant No. 7966. hormone supplied by the Roussel Corporation assayed at 7,000 I.U. per milligram and was prepared from human pregnancy urine.

Five milligrams of this preparation in 5 ml. of normal saline was further purified by the adsorption of associated glycoproteins on an anionic resin in a borate form as described by Butt and Round.8 Amberlite IRA 400 (OH) resin was first washed in normal NaOH, normal NaCl, and water and the fines removed; then a borate buffer made up to pH 7.0 from mixtures of boric acid (0.1M) and sodium borate (0.05M) was used to convert the resin to its borate form. One half gram of the air-dried borate resin was added to the 5 ml. of dissolved hormone, shaken for 10 minutes, and the resin removed by filtration. The final volume was 4 ml. The activity was increased to approximately 8,000 to 9,000 I.U. per milligram, and this purified hormone was used as the antigen.

2. Preparation of the antigen in "Freund's adjuvant." Two milliliters of antigen solution (14,000 I.U.), 2 ml. of Bayol-F,* 1 ml. of Falba† (heated until just liquid), and 3 mg. of finely powdered Mycobacterium butyricum were mixed by vigorous stirring.

An antigen was also prepared with neutralized aluminum chloride but this alumprecipitated hormone proved to be a relatively ineffective antigen.

3. Experimental animals. Four young adult virgin female albino rabbits weighing

^{*}Light paraffin oil distributed by Stanco Distributors Inc.

[†]An absorption base distributed by Pfaltz & Bauer, Inc.

slim line of precipitation forms at the interface if the hormone antigen is present. The time of appearance of the precipitin ring is directly related to the concentration of the dissolved hormone (Fig. 1).

initially 3 to 3.5 kilograms were used to develop the antisera. On the possibility that the end organ might play some role in the rapid disappearance of HCG from the circulation of female rabbits,⁹ 2 of the animals were ovariectomized one month prior to the antigen injections. The rabbits were maintained on rabbit pellets supplemented with fresh greens twice a week.

4. Development of antiserum. One half milliliter of the above antigen was injected into each of the rear foot pads of the 4 rabbits. On alternate weeks, beginning 2 weeks after the initial injections into the foot pads, 3 booster injections (1 ml.) consisting of the same ion-exchanged antigen, in this case suspended in saline rather than the adjuvant (3 mg. in 6 ml. of saline), were given intravenously. The animals were exsanguinated by cardiac puncture under ether anesthesia one week after the final injection. Alternatively, 30 ml. of blood may be writhdrawn without sacrificing the animal, and the antibody levels determined serially at weekly intively, 30 ml. of blood may be withdrawn antisera per rabbit was the average yield from exsanguination. For convenience, the antisera is stored in 2 to 5 ml. aliquots (with or without Merthiolate 1:10,000) at -20° C. No deterioration was observed over a 2 month period, under these conditions, provided the thawed antiserum was not refrozen.

5. Preparation of urinary extracts from nonpregnant women. Urinary extracts from nonpregnant, 2 weeks postpartum, 3 weeks postpartum, and menopausal women were made. These were prepared by a method based on the adsorption of the hormone with benzoic acid and precipitation with alcohol, a technique employed by the manufacturer (Roussel) to prepare the hormone commercially.

6. Precipitin testing procedure. The standard precipitin testing technique¹⁰ was performed in 2 by 15 mm. microtest tubes which are scrupulously clean and unscratched. The reaction is carried out at 25 to 27° C. The denser antibody phase is carefully overlaid with the test solution by means of a 24 gauge, 1½ inch needle and tuberculin syringe. A

Purity of antibody

The urinary extracts, nonpregnant and 3 weeks postpartum, both gave negative results by the precipitin technique described above. There was a faintly positive reaction to extracts of the 2 weeks postpartum urines. Other less pure preparations of HCG antiserum produced antibodies which reacted with all the urinary extracts.

The serum-agar technique of Ouchterlony¹¹ demonstrated a single precipitin line after one week. This is suggestive of a specific antiserum. Previously, less pure antibody preparations produced to 2 to 3 such lines in the agar plates.

Human albumin, gamma globulin, and C-reactive protein all gave negative precipitin reactions.

One of four menopausal urines with high titers of follicle-stimulating hormones (FSH) and presumably high luteotrophic hormone (LH) levels did, however, give a faint precipitin ring (after 2 hours), as did a single urine specimen from a castrated male. It is unlikely that the small amounts of FSH and LH contaminating the original antigen produced titer of antibodies against these hor-

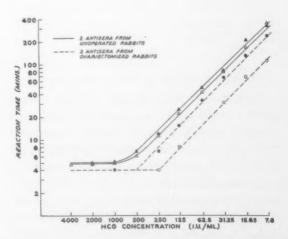


Fig 1. Time-concentration relationship of HCG antibody.

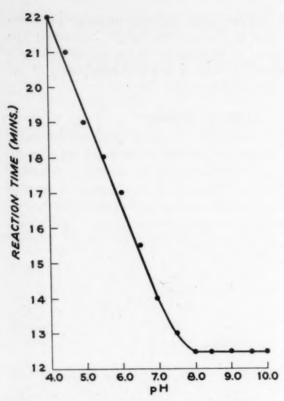


Fig. 2. pH effect. (Concentration of HCG, 195 I.U. per milliliter.)

mones indetectable by the Ouchterlony technique. There is, however, the possibility of a cross-reaction between these chemically simlar gonadotrophins which cannot be ruled out. There may be several antigenic moieties in the same compound detectable only in liquid media. With highly purified human FSH and LH preparations it should be possible to test for contaminating antibodies to these components. Such preparations were not available to us.

Standardization of the antiserum

Known concentrations of purified antigen were diluted in urine at pH 8.0 and then plotted against time of appearance of the precipitin ring on semilogarithmic graph paper. This gave a linear relationship within experimental limits. Each antiserum, depending upon its potency, assumes a characteristic time-concentration curve. The 4 antisera tested produced a family of parallel curves (Fig. 1). It will be noted that the antisera

from the 2 ovariectomized animals appear to possess slightly higher antibody titers. Additional studies are necessary to confirm this possibility.

In a concentration equivalent to a high urinary titer of chorionic gonadotrophin (400,000 I.U. per liter) the precipitin ring appeared in 5 to 6 minutes.

The lower limit of sensitivity of the immunological assay depends primarily on the potency of the antiserum, but is not below 8 I.U. per milliliter (1 µg of HCG per milliliter). In our hands the Aschheim-Zondek assay¹³ can detect as little as 5 I.U. per milliliter of a similar preparation. The Friedman assay¹⁴ is of the same order of sensitivity as the antibody method.

The effect of pH. Small amounts of normal HCl or NaOH were added progressively to urine of known hormonal constituency, starting at pH 7.0, and the time of precipitin formation noted at each pH from 4 to 10. The dilution factor was found to have a negligible effect on the reaction time.

Results. Below pH 7.0 there was a gradual increase in the reaction time (Fig. 2). Between pH 7.0 and 9.0 there was a slight decrease in the times. Above 8.5 a nonspecific precipitate appeared in the supernate. The optimal pH appears to be approximately 8.0.

The effect of salt concentration. Starting

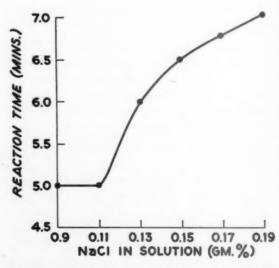


Fig. 3. Salt effect. (Concentration of HCG, 370 I.U. per milliliter.)

with normal NaCl solution of chorionic gonadotrophin (368 I.U. per milliliter), small increments of solid NaCl were added progressively and aliquots tested until the salinity was above 2N.

Results. Over 1.3 mg. per 100 ml. of NaCl produced gradual inhibition of the precipitin reaction (Fig. 3). The average NaCl concentration of urine is 1.4 mg. per 100 ml.

Neutralization of biological activity

To test the ability of the antibody to inactivate HCG, 0.5 ml. each of the following solutions was injected into 21-day-old female mice: (A) 136 I.U. per milliliter of chorionic gonadotrophin in saline with an equal volume of antiserum (34 I.U. per 0.5 ml.); (Ap) the washed precipitate was suspended in 0.5 ml. saline; (B) 136 I.U. per milliliter in normal saline with an equal volume of control rabbit serum (34 I.U. per 0.5 ml.); (C) normal saline with an equal volume of antiserum.

All solutions were allowed to stand at room temperature for 3 hours, then at 0° C. for 36 hours. All were centrifuged and the supernates (A, B, and C) injected into the mice. The precipitate (Ap) containing the hormone-antibody complex was also injected. No corpora lutea were observed in the fractions from either solution A, Ap, or C, while B showed prominent luteinization.

Qualitative test for human chorionic gonadotrophin

Procedure. The urine to be tested must be diluted 4 parts urine to 1 part distilled water, unless below 1.020 specific gravity, to decrease the NaCl concentration and maintain separation of the antigen and antibody phases. The above dilution will reduce urinary specific gravity from 1.024 to 1.020. The urine is initially brought to pH 7.8 to 8.0 with normal NaOH (less than 0.3 ml. per 10 ml. of urine). The urine is centrifuged or filtered until crystal clear in order to avoid nonspecific precipitation. The antiserum is normally at pH 8.0. The test is carried out as described under "Precipitin testing" approximately 0.05 ml. of antiserum and 0.05 ml. of the test urine. A control is run with each specimen with normal rabbit serum substituted for the antiserum.

The test is read at 1, 2, 3, and 4 hours. To be read as positive, a test must show reaction by the end of the second hour. This eliminates contaminating antigens in low concentration, which occasionally react after that length of time. However, it would also eliminate urines which are HCG positive in low dilution (8 to 16 I.U. per milliliter). Therefore, 2 ml. of late reacting urine is routinely injected for the Aschheim-Zondek bioassay¹³ to detect low concentrations. To date none of these has been positive. Duplicate samples were tested simultaneously by both the immunological assay and the Friedman method for chorionic gonadotrophin. The samples represent unselected urines received by Central Laboratories at the University of California Medical Center from March 18 to May 15, 1959.

Results. The 2 hour test results are compiled in Table I. Where the two methods disagreed, the Aschheim-Zondek assay with 3 mice was employed as a confirmatory test with 2 ml. of the undiluted urine (Table I).

There were 40 additional tests on specimens known to be positive for chorionic gonadotrophin. All proved to be positive with the antibody technique.

Twenty-five control urines from 5 normal males and 20 nongravid young adult females were antibody negative.

Comment

The simplicity and speed of the immunoassay as well as its usefulness in the face of bacterial contamination are apparent. Its clinical reliability is strongly suggested by the above data but awaits more extensive trials.

Modification of this technique to provide a quantitative assay will probably require extraction of HCG from the urine, e.g., kaolin or benzoic acid, which will also eliminate interfering electrolytes, and treatment with the borate resin to remove contaminating glycoproteins and assure reproducible results. Salting out with ammonium sulfate and sodium sulfate15 offers an alternative means of puri-

Table I

Assay method	Test results		False results*	
	Positive	Negative	Positive	Negative
Friedman	18	19	1†	2
Immu- nological	19‡	20‡	0	0

*The Aschheim-Zondek assay was used as the decisive test.

†The false-positive Friedman test was performed on the urine of a 40-year-old man with a testicular tumor and gonadal atrophy.

‡Two of the urine specimens were toxic to both rabbits and mice. Immunoassays were performed successfully.

fication. The hormone-containing extract may then be tested for a precipitin ring formation by the progressive dilution technique employed by Hayashida⁴ for rough quantitation of growth hormone or by extrapolating from the time-concentration curve used by Chernoff¹⁶ for assaying small amounts of fetal hemoglobin. More precise determinations are possible by measuring the amount of precipitation in the zone of optimal proportions. An alternative to the precipitin reaction is the detection of agglutinating antibodies to HCG by adsorption on "tanned" red blood cells or latex particles,

a technique used for assaying growth hormone.17

Summary

A method for the development of a relatively pure and potent antiserum against human chorionic gonadotrophin is described. A qualitative immunoassay, using this antiserum, is compared with the Friedman bioassay. The immunological technique, which may be read in 2 hours, compares favorably with respect to sensitivity and reliability.

I am indebted to the Roussel Corporation of New York, New York, for their gift of purified human chorionic gonadotrophin and for their cooperation on this study.

The help and cooperation of Dr. Ludmila Gramadski, in the Endocrine Laboratory of Central Laboratories, greatly facilitated the comparative studies of the immunoassay with the Friedman test.

I am indebted also to Dr. Tetsuo Hayashida, whose advice helped to guide these investigations, to Dr. James Merrill, whose laboratory prepared the ovarian tissue sections for the antibody neutralization studies, and to Dr. Ernest W. Page, in whose laboratory these investigations were performed, for his help and encouragement.

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CURRENT OPINION

Clinical problems

Thyrotoxicosis and pregnancy

Case presentation

Mrs. V. R., a 23-year-old white married woman, gravida v, para iv, was first seen on Feb. 23, 1960, and was admitted to the hospital. Her last normal menstrual period was July 7, 1959; the estimated date of confinement was April 14, 1960.

Three months prior to admission the patient first noticed the onset of nervousness and an increase in irritability. This was followed by the occurrence of a tremor, increased sweating, increased appetite, and initially some weight loss. She then developed a marked heat intolerance, edema of the legs and feet, ease of fatigue, insomnia, diarrhea, and blurring of vision. She also noticed an increase in collar size.

Past history. The patient's first 3 pregnancies were uncomplicated and resulted in normal spontaneous deliveries. The fourth pregnancy ended with the delivery of a still-born infant during the eighth month in May, 1959.

Physical examination. The patient's weight was 153 pounds, her height 5 feet, $3\frac{1}{2}$ inches. The blood pressure was 200/0; pulse, 140 per minute; and respirations, 35 per minute and labored. The temperature was normal. The patient was very irritable, and she had a marked gross and fine tremor. Pulsations were visible over most of the body. The skin was warm and moist and the hair was very fine and silky.

Examination of the eyes revealed an increased palpebral fissure, slight exophthalmus, lack of convergence, but no lid lag.

The thyroid was diffusely and smoothly enlarged. A distinct bruit was audible over the gland with a stethoscope. The lungs were clear to auscultation and percussion. The examination of the heart revealed the point of maximal impulse to be $2\frac{1}{2}$ cm. outside the mid-clavicular line. There was a systolic thrill palpable over the apex and along the left sternal border. A Grade II systolic murmur was heard at the aortic area and at the left sternal border at the level of the third intercostal space. P_2 was greater than A_2 .

Abdominal examination demonstrated the liver to be tender and down one finger-breadth below the right costal margin. The height of the fundus was 18 cm. above the symphysis. Fetal heart tones were present. The right side of the uterus was tender. There was 3-plus edema of the feet and lower legs. The reflexes were hyperactive.

Laboratory tests and results. The erythrocyte count was 3.2 million, hemoglobin, 7.0 Gm. per cent, and the hematocrit determination 24 per cent. The leukocyte count was 7,650 with a normal differential, including 2.5 eosinophils. The blood smear showed 3-plus hypochromia, 1-plus target cells, and 2-plus anisocytosis. Examination of the urine revealed a 2-plus albuminuria, negative sugar, and a specific gravity of 1.022. The fasting blood sugar level was 71 mg. per cent, the blood urea nitrogen level 14.1 mg. per cent. The protein-bound iodine was too high to read, or at least 20 µg. The butyl extractable

iodine was 14 μ g. The basal metabolic rate was plus 94 per cent. The iodine¹³¹ uptake was 52 per cent in 22 hours and the conversion ratio, 71.3. The total serum protein was 4.29 Gm., the albumin being 2.42 Gm.

Problem: Would you discuss in general the management of thyrotoxicosis during pregnancy and the management of this patient in particular.

Consultation

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Knowledge of the altered production, transport, and utilization of thyroid hormone in pregnancy is at present incomplete. In consequence, management of cases of thyroid dysfunction in pregnancy is in part rational, based on available facts, and in part empirical, depending upon individual experience. The surgeon offers subtotal thyroidectomy and the internist antithyroid drug therapy which each claims to be ideal for the pregnant thyrotoxic patient. Yet both treatments are merely crudely "antithyroid" and, until a drug is available which corrects the specific disorder of thyroid metabolism underlying thyrotoxicosis, the relative merits and applications of surgical and medical treatment are likely to be in dispute.

Thyrotoxicosis in pregnancy is commonly diagnosed, or at least suspected, by the obstetrician and the mode of treatment will largely depend upon the particular colleague to whom he refers the patient. Accordingly, this step must be made with due deliberation. This, of course, is assuming that the thyrotoxicosis is recognized in early pregnancy; uncontrolled thyrotoxicosis in late pregnancy offers little choice of therapy.

If the condition is diagnosed early, my choice is for the patient to be put under the care of a thyroid surgeon or a medicalsurgical team practicing subtotal thyroidectomy in pregnancy after preliminary drug therapy. This preference is in part based upon favorable experience with such management, but in addition there seems to be rational support for it.

First, during pregnancy the patient with thyrotoxicosis tends naturally to revert toward euthyroidism. An explanation of this apparent contradiction to the increased activity of the thyroid gland in pregnancy is offered by the finding of a disproportionately raised thyroxin-binding capacity of the maternal serum. The increased thyroxin output is apparently bound to globulin and in this form is relatively inactive. However, as might be expected from these facts, thyrotoxicosis is frequently worse after pregnancy. This may be a great handicap at the time the mother is most needed by her baby. If operation has been performed such relapse is less common. Second, although the usual tendency during pregnancy is toward improvement, it is not surprising in view of the complex physiologic adjustments taking place that unpredicted exacerbations are not infrequent. In addition, delivery per vaginam or by cesarean section is a severe stress phenomenon which may provoke a thyroid crisis. Such episodes are much less likely to be a concern after thyroidectomy. Finally, in the occasional case where thyroidectomy fails to control the condition completely, drug therapy may be resorted to in late pregnancy. The converse is not true—by the time it becomes evident that antithyroid drugs are not effective, operation is usually out of the question because of the advanced stage of the pregnancy. This "belt and braces" argument probably has little appeal to the internist or surgeon impressed by the elegance of his particular therapy but to the obstetrician, whose prime concern is the mother's safety, it has strong appeal.

Thus, the "comfortable middle trimester" of pregnancy would seem from many points of view an optimal time for thyroid operation. This idea, of course, has to be "sold" to the patient whose initial emotional response is usually against operation. When it is explained that the operation is most unlikely to disturb the pregnancy, that it

offers the best chance of permanent cure, and that she can expect to be free from medical care and fit to tend her baby after delivery, she is usually converted to the idea.

In fairness to the drugs now available, it must be said that they have contributed greatly to the present safety of surgery in pregnant thyrotoxic patients. It is also true that in carefully controlled dosage, any risk of damage to the fetal thyroid is negligible and may be discounted except in cases of severe thyrotoxicosis in late pregnancy when large doses may have to be given in order to safeguard the mother's life. This is no argument against the drugs for they offer the only hope in these circumstances.

Choice of antithyroid drug requires some consideration. Many reputable centers use different thiouracils and imidazoles, which suggests that there is little to choose between the various preparations. Recently, however, a rival drug has entered the field—the simple inorganic substance potassium perchlorate. This is being used increasingly in Europe, with most satisfactory results, in both pregnant and nonpregnant patients. It acts by interfering with the iodine-trapping mechanism of the thyroid gland. It is just as likely to affect the fetal thyroid as any other antithyroid drug if given in late pregnancy in uncontrolled dosage and does have its quota of side effects but these are no more troublesome than those of the other drugs available. Care must be taken during this treatment to avoid an excessively high iodine dietary intake. Restriction of foodstuffs is not necessary but a check must be made for iodine-containing vitamin preparations and cough mixtures. One feature which should have universal appeal is that the daily dosage cost is approximately one fifteenth that of the organic preparations used.

Assessment of response to therapy is difficult in pregnancy, and clinical assessment with particular emphasis on the pulse rate during sleep is at least as important as any laboratory test. Of these tests, the proteinbound iodine (PBI) is probably the most valuable in pregnancy. In the interpretation of signs and tests, allowance must always be made for the normal effects of pregnancy. The PBI, like most other parameters of thyroid function, gives elevated readings in normal pregnancy. The aim should be to undertreat rather than the reverse and, if operation is not performed, to try to withdraw or reduce the dose of the antithyroid drug during the few weeks before term.

In our experience severe anemia, which occurs in the case described, is common in thyrotoxic pregnant patients and is frequently of megaloblastic type. Folic acid is rapidly excreted in hyperthyroidism and this, combined with malabsorption due to the intestinal hurry and the large fetal demand for folic acid, adequately explains the etiology. It is therefore advisable to administer folic acid supplements to these patients without waiting for the development of frank megaloblastic change in the marrow which may occur only after failure of prolonged iron therapy and when the pregnancy is dangerously far advanced.

With regard to delivery, spontaneous labor with assisted vaginal delivery in the second stage is ideal. Cesarean section is not indicated per se but, as with cardiac patients, if the circumstances are such that any degree of difficulty in labor is envisaged, elective cesarean section is preferable to the prospect of having to perform the operation after the patient is exhausted by labor.

In the case described, it is obvious from the clinical picture alone that there is severe thyrotoxicosis with commencing cardiac failure and that urgent therapy is indicated. Albuminuria and edema with hypertension in late pregnancy are rather automatically taken to mean toxemia. Although it has been claimed that toxemia occurs with increased frequency in pregnant thyrotoxic patients, this is not clearly substantiated. The albuminuria and edema may merely be secondary to the severe thyrotoxic process with cardiac failure and may be expected to clear with antithyroid therapy. In the case described it seems very probable that this is the situation. Another factor contributing to the cardiac strain is the gross anemia. As mentioned, this is common in thyrotoxic pregnant patients and, although the findings recorded are of iron-deficiency anemia, I would give folic acid, 5 mg. three times a day, in addition to iron intravenously as the saccharated oxide in divided doses to a total of at least 1,200 mg.

My management of the thyrotoxicosis would depend on whether the pregnancy is as far advanced as the period of amenorrhea suggests (33 weeks) or whether it corresponds with the fundal height-approximately 10 weeks less. It is possible that amenorrhea was the first symptom of the thyrotoxicosis and that conception occurred only after a period of pathologic amenorrhea. When were fetal movements first experienced and is there information about any early pregnancy examinations performed elsewhere? Radiologic assessment of the fetal skeleton would also be helpful and, under these circumstances, fully justified. The other point on which information would be desirable is the cause of the stillbirth in the preceding pregnancy. Was there evidence of toxemia or anything in retrospect at all suggestive of commencing metabolic disorder? If this was not the case it is tempting to conclude that the mental shock associated with the stillbirth was of significance in the development of the thyrotoxicosis.

If the evidence suggests that the duration of pregnancy corresponds with the period of amenorrhea, I would rely entirely upon medical management. In fact, even with intensive treatment it is going to be something of a race against time to get the thyrotoxicosis under reasonable control before labor commences.

Strict bed rest in the hospital is essential and should be augmented with amobarbital (Amytal), 150 mg. thrice daily. I would give potassium perchlorate, 1,000 mg. per day, as the specific antithyroid therapy. If the response seemed slow, the dose might later be increased to 1,500 mg. per day but this would carry an increased risk of side effects. The other type of drug which might be expected to benefit the immediate situation would be a saluretic such as hydrochloro-

thiazide, 25 mg. three times a day for 4 days, followed by further courses if necessary.

If the response to this therapy is favorable and rapid, the potassium perchlorate may be withdrawn or the dosage reduced after 38 weeks, but, if control is not achieved by then, the drug must be continued and the fetal risk ignored for the mother's life is in danger if labor occurs while the thyrotoxicosis is still uncontrolled.

After delivery, lactation must be suppressed as antithyroid drugs are excreted in the milk. The baby must be carefully assessed clinically for evidence of thyroid deficiency. A PBI estimation on the cord blood is of value if compared with a repeat estimation at 2 to 3 weeks, a considerable drop suggesting impaired fetal thyroid function.

Alternatively, if investigation suggests that the pregnancy is less far advanced than the dates suggest and more in accord with the uterine size I would institute similar medical treatment but hope that, if reasonable control is achieved after 6 to 8 weeks, subtotal thyroidectomy be performed. In these circumstances the choice of antithyroid drug and whether Lugol's iodine should be given in the immediate preoperative period are decisions properly referred to the surgeon who is to perform the operation.

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Thyrotoxicosis occurring during pregnancy is usually due to Graves' disease or hyperthyroidism accompanied by diffuse hyperplasia of the thyroid, but may occasionally be due to Plummer's disease, or hyperthyroidism with thyroid adenomas. The diagnosis of Graves' disease in this patient is incontrovertable, but it is well to review the normal changes in thyroid function and tests which occur in pregnancy since they are pertinent to the diagnosis of borderline hyperthyroidism in pregnancy and particu-

larly to the management of a patient of the type presented. Normally, an increase in thyroid size occurs during pregnancy, accompanied by a 15 to 20 per cent increase in basal metabolic rate from prepregnant values. The uterus and fetus account for 70 to 80 per cent of the increased oxygen consumption, with the remainder due to increased work of the maternal heart and increased work of respiration due to mechanical interference. The serum protein-bound iodine (PBI) or butanol-extractable iodine (BEI) also rises during pregnancy, the former ranging between 6 and 13 µg per cent but showing a mean rise of approximately 50 per cent, due to an increase in thyroxine-binding globulin (TBG). There are few studies of thyroid function with I181 during pregnancy, but there apparently is some increased avidity for iodine by the thyroid in pregnancy. Study of two series1, 2 of fetuses obtained by therapeutic abortion have indicated that uptake of I181 by the fetal thyroid occurs between the twelfth and fourteenth weeks of pregnancy, and that fetal elaboration of thyroid hormone occurs around the nineteenth week.

In the management of hyperthyroidism during pregnancy two principles may be initially stated:

- 1. The use of therapeutic I¹³¹ is agreed to be contraindicated by all observers because of the fetal uptake. Three patients, however, have inadvertently been given I¹³¹ at a time when the fetus could accumulate iodine, but in each instance they had normal babies.²
- 2. Production of a viable fetus is a prime consideration for surgeon and internist alike. Essentially, there are two therapeutic choices, the use of antithyroid compounds alone to control the hyperthyroidism, or the use of antithyroid compounds followed by subtotal thyroidectomy. There are many reported series of medically managed patients without fetal loss, or occurrence of fetal goiter or cretinism, which are usually compared to surgically treated patients with a high fetal loss. Fetal loss is usually attributed to transient postoperative hypothyroidism.

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In addition, there are many series of surgically treated patients without fetal loss which are usually compared to medically managed patients with a high occurrence of fetal thyroid enlargement, tracheal compression and respiratory distress, and cretinism. However, a review³ of the reported series of fetal thyroid enlargement noted that this has occurred in normal, hypothyroid, and hyperthyroid mothers, that it has occurred after no treatment, after operation prior to the pregnancy, and after the use of thiouracil derivatives or iodide. With one exception, however, fetal goiter was found only after treatment of a thyrotoxic mother with thiouracil derivatives or iodide. Most of the surgically treated patients have had thyroidectomy during the second trimester of pregnancy, due to the increased possibility of abortion during the first trimester, and a willingness to wait until after delivery during the third trimester. However, since it is necessary to bring the patient to euthyroid levels of function prior to operation at any stage of pregnancy, one wonders if surgical therapy of such a euthyroid patient is not superfluous.

In this particular patient it would be preferable to use propylthiouracil, or methimazole, and iodides in sufficient dosage to control the hyperthyroidism until delivery. Both maternal thyroxine and thiouracil derivatives have been shown to traverse the placental barrier. In addition, the thiouracil derivatives are present in breast milk, contraindicating nursing during the administration of antithyroid compound. Since one wishes to avoid fetal goiter and since these patients usually respond well to small doses, thiouracil derivatives should not be given in large amounts until a normal BMR and PBI are obtained, but only in sufficient dosage to control the symptoms and return these determinations to the normally elevated values of the pregnant woman. Since iodides have been repeatedly demonstrated to control or reverse the thyroid hyperplasia produced by thiouracil derivatives, it would be preferable to also give iodide to prevent fetal and maternal thyroid hyperplasia, recognizing that the serum PBI therefore cannot be used as an index of control. The
presence of an extremely wide pulse pressure, probable cardiomegaly, a thrill, systolic
murmur, hepatomegaly, and edema would
suggest that the high output cardiac failure
of hyperthyroidism, with the decreased peripheral resistance of hyperthyroidism augmented by the effective placental arteriovenous shunt, may be present and would
warrant further study of the patient.

Of great interest is the light that this combined situation throws upon the etiology of hyperthyroidism. There are 9 reported instances4 of neonatal hyperthyroidism, 8 of which occurred in infants of mothers with inadequately treated or nontreated hyperthyroidism and one in a mother with only partially treated hypothyroidism. In one additional patient onset occurred 5 days after delivery, at a time when maternal antithyroid medication effect upon the infant would be subsiding. In 8 instances the fetal thyroid enlargement and symptoms of hyperthyroidism disappeared spontaneously during treatment after 2 to 6 weeks. There has not been convincing evidence of increased elaboration of thyrotrophic hormone in hyperthyroidism, but recently Adams⁵ and McKenzie⁶ have presented convincing evidence of the presence of a factor in the sera of hyperthyroid patients which increases the thyroidal I131 uptake of mice after a delay of 8 to 12 hours instead of a delay of 4 hours for thyrotrophin. Interestingly, as in the hyperthyroid patient, this response is not suppressed by prior feeding of desiccated thyroid.

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During the last decade considerable attention has been given to the medical control of thyrotoxicosis. With the advent of the thiourea derivatives not only have patients been better prepared for the classical subtotal thyroidectomy but in many instances long-term management in selected cases has been successful without operation. Radioactive iodine has further strengthened the position of medical management to the exclusion of surgery, especially in Graves' disease, or nonnodular hyperthyroidism. Failure to control hyperthyroidism has been recorded for all modalities of treatment, but where one method has failed the other usually has solved the problem. While we recognize the fact that the medical efforts to control this problem represent a substantial advance, the shortcomings and complications of antithyroid drugs are such that operation remains the treatment of first choice in certain instances, and one of these is thyrotoxicosis during pregnancy.1-3, 7, 9, 22, 26 When the pregnant patient's symptoms are brought under prompt control with suitable antithyroid preparation and then she undergoes subtotal thyroidectomy, the thyrotoxicosis is uniformly eliminated and fetal wastage is reduced to a bare minimum. A current report in this regard from Bell and his associates³ indicates that in their last 21 patients this condition has been very well controlled in this manner with only one fetal loss, and it was believed that the thyroid status of the mother played no role in this particular instance. All infants were normal at birth and developed normally thereafter. It appears that not only are there more live infants obtained with such a program, but also the possible deleterious effects of drug-induced fetal hypothyroidism are avoided.8

In order to properly enlarge upon our stand in this matter perhaps we should review some of the specific problems that arise in pregnancy complicated by thyroe

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toxicosis. Although this is a rather uncommon situation it is known to be a serious threat to the gravid woman and her fetus. In the experimental laboratory, thyrotoxic abortion has been demonstrated to be common in the rat, guinea pig, and rabbit. 12, 17, 22, 23, 27 Prior to modern treatment, Seitz reported in 1913, from a collected series of 112 patients, that not only did 7 women die, but numerous complications occurred, such as spontaneous abortion in excess of the usual expectancy, premature labors, stillbirths, and violent labors.32 In more recent years it has been stated that pregnancy in hyperthyroid patients terminates in fetal losses as high as 50 per cent, while others have contended that these complications are only slightly more frequent in the presence of hyperthyroidism than in normal pregnancy.2, 5, 7, 21, 26 Although these opinions may be diverse, there is general agreement that prompt control of the hyperthyroidism is desirable in order to eliminate whatever causative influence this may have on the incidence of these complications.

When we turn our attention to the effect of hyperthyroidism on the fetus, we learn that the weight of evidence indicates that hyperthyroidism probably does not directly harm the surviving fetus.5, 7, 26 The infants successfully delivered at term under these trying circumstances have all been physically normal when not otherwise altered by prolonged medical management. In contrast, there are strong indications that medical management with radioactive iodine or the thiourea derivatives, directly as well as indirectly, results in mild to serious defects in the developing fetus.2, 8, 10, 11, 16, 84 Both of these substances readily pass across the placental barrier and depress the fetal thyroid in various ways.4, 18, 14

While the use of radioactive iodine as a diagnostic as well as therapeutic modality has been a significant medical advance, its damaging effect upon the fetus is a matter of record.^{14, 34} Significant amounts have been found in the human fetal thyroid by the twelfth week of gestation.⁴ Russell and

his colleagues⁸⁰ have reported the administration of I131 to 2 pregnant women with thyroid cancer and both delivered infants with true congenital hypothyroidism. One of the newborn infants died at the age of 3 months, and no thyroid tissue was found at autopsy. Valensi³³ has reported cretinism in an infant born to a woman with thyrotoxicosis treated in the second trimester with radioactive iodine. In addition to these observations, the ages of the pregnant patient and her fetus are such as to make the use of I131 a hazard in regard to possible carcinogenic effects as well as the possibility of mutation of genes from gonadal irradiation. It appears then that the use of I131 is rather clearly contraindicated in pregnancy.

While thiouracil compounds have been used successfully throughout pregnancy in many cases, Krementz and his associates²² have recently reviewed the literature and report that, of 75 infants born under these circumstances, 18 demonstrated abnormalities related to the goitrogenic drugs: abortion, severe hypothyroidism, transient goiter, delayed ossification, retarded growth and serious thyroid hypertrophy. While cretinism is an extremely rare development, transient neonatal goiters have been described with greater frequency.15, 25, 31 Some have been described as asymptomatic, but others have caused serious respiratory difficulties, even to the extent of causing death by tracheal obstruction in an otherwise normal infant. In such cases the thyroid has been found to be enlarged with hyperplasia of the acini accompanied by increased fibrous tissue overgrowth, which is basically the same as is found in the adult.15, 20

As these complications of antithyroid drug therapy have become better known, efforts have been made to overcome some of the disagreeable end results by reducing the dosage of the drugs or by adding desiccated thyroid substance to the program. For example, the administration of thiouracil to pregnant rats and guinea pigs produces enlargement and hyperplasia of

the thyroid gland and retarded growth in the offspring, but these abnormalities disappear when the drug is discontinued. 10, 11, 17 On the other hand, dosage and length of therapy are known to be directly related to drug effectiveness as far as the thyrotoxicosis is concerned. This dilemma was well demonstrated by the experience of Piper and Rosen²⁸ who discontinued the drugs at the sixth and seventh months of gestation in order to avoid untoward effects in the fetus. In 16 patients so treated, the fetal mortality rate was 31 per cent and the hyperthyroidism recurred in 84 per cent of the mothers.

As one reviews the numerous problems related to the use of the thiourea derivatives in pregnancy complicated by hyperthyroidism, the position of these drugs becomes rather precarious. It seems evident from the collected data that there is considerable agreement regarding the necessity of maintaining adequate amounts of thyroid hormone in the maternal blood stream not only to support the pregnancy but also to produce a normal infant. In addition, the ideal therapeutic goal must include the avoidance of induced fetal hypothyroidism while achieving control of the maternal thyrotoxic state. In view of all these facts and because prolonged administration of these goitrogenic drugs has been correlated with the highest incidence of fetal loss, one is led to conclude that their greatest practical value in pregnancy lies in their known effectiveness as preparatory agents for subtotal thyroidectomy.22 With this plan a short course of Lugol's solution should be added to the regimen during the 2 weeks immediately preceding operation, as is usual in nonpregnant individuals with Graves' disease. Following the thyroidectomy it is logical to assume that the patient's thyroid function has been reduced to a level somewhat lower than is adequate for the fetus as well as for the pregnancy and for this reason from 60 to 120 mg. of desiccated thyroid plus 1 or 2 drops of Lugol's solution should be administered daily. This program has proved to be a practical solution to this problem with the fetal loss reduced to 4.7 per cent, a rate which approximates the frequency of fetal loss in uncomplicated pregnancies.^{1, 3, 19}

Anesthesia has been no serious problem for these patients. The ideal as well as most common time for operation is the second trimester since transient fetal hypoxia, if any, is better tolerated after the third or fourth month of gestation. These patients have required a relatively short period of hospitalization and can be permitted to return to their usual household duties within 2 or 3 weeks after operation. Because of the fact that maternal hypothyroidism is accompanied by an increased incidence of toxemia of pregnancy, abortion, and fetal abnormalities, considerable care must be given to the continued administration of desiccated thyroid substance. It is very effective for the continuation of a normal pregnancy in these postsurgical patients and its dosage should be carefully regulated to maintain the metabolic rate within the range of high normal.3 Because of the differences in placental transfer rates such fetal protection appears to be more likely achieved after subtotal thyroidectomy than when given in conjunction with the thiourea derivatives,1, 2, 27

With reference to the present patient, it is apparent that she is now 2 months from term and in a very serious state of thyrotoxicosis. She is an obvious candidate for hospital care in order to treat most effectively the 3 more serious complications that might arise at this time: thyroid crisis, premature labor in the presence of uncontrolled hyperthyroidism, and eclamptogenic toxemia. In my opinion her present status is really that of impending or early crisis and the immediate management should be planned with this complication foremost in mind. Large doses of iodine, antithyroid compound (Tapazole), and sedatives should be administered simultaneously in the hope that the toxicity can be brought under control as quickly as possible. One of the cortisone preparations may also be necessary if adrenal deficiency becomes a more obvious factor. If steady improvement occurs over a period of 3 to 4 weeks, the iodine dosage can be gradually reduced as the Tapazole becomes more effective. The patient eventually can be maintained during the last weeks of pregnancy on the thiourea derivative alone since she is so close to term. After delivery the medical management should be continued until such time as it is thought appropriate for her to undergo definitive subtotal thyroidectomy.

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Editor's comment

The patient was put in a dark room at complete bed rest and given phenobarbital and reserpine (Serpasil) intramuscularly. She responded to this treatment with a decrease in the signs of hyperactivity and a slight decrease in pulse rate to 120. The blood pressure remained between 190/70 and 190/0. She was given a high protein, high carbohydrate, low sodium diet.

The next day the patient was started on Lugol's solution, methimazole (Tapazole) and chlorothiazide (Diuril). During the day she started to spot blood vaginally and the fetal heart tones which were heard the day before were now absent. The uterus was tender on the right side. Shortly thereafter uterine contractions started and the patient was delivered of a 4 pound, 11 ounce stillborn infant. There was no evidence of abruptio placentae.

The patient was given 3 units of blood, 2 of them packed cells. Following the transfusions the hematocrit determination was 40. Eleven days after the delivery the patient was taken off Lugol's solution and methimazole. At this time the pulse was 85 and the blood pressure was 110/54. The

butanol extractable iodine was normal and the patient was resting well and showing only slight signs of hyperactivity. Ten days later I¹⁸¹ uptake was 82 per cent in 24 hours and the conversion ratio still 72. The next day the patient was given 9 mc. I¹³¹ orally. Two days later Lugol's solution was again started.

One week later she was discharged from the hospital on Lugol's solution, a high carbohydrate diet, and continued bed rest. Minor symptoms of increased thyroid activity were present. The patient had a slight tremor and increased perspiration. The pulse was about 95; the blood pressure was normal. The heart had returned to normal size and no murmurs could be heard. The thyroid gland had decreased slightly in size and no bruit could be heard. There were no obstetric complications during the post-partum course.

Reviews Abstracts

Edited by

LOUIS M. HELLMAN, M.D.

Reviews of new books

Typical Gynecologic Operations. By Siegfried Tapfer, translated by L. M. Szamek. First English edition. 81 pages, 168 figures. Philadelphia, 1960, J. B. Lippincott Company. \$9.00.

In the author's foreword he states it is his intention to point up some technical advantages of which the surgeon can avail himself in performing the operations selected for inclusion. Dr. Tapfer's exposure to several European schools of surgical technique has resulted in the inclusion of many of these ideas in his book.

The operations selected are supravaginal amputation of the uterus, total abdominal hysterectomy, the Wertheim type of radical abdominal hysterectomy, anterior and posterior vaginal plastic operations, the Fothergill operation, vaginal hysterectomy of Schauta, and the surgical treatment of carcinoma of the yulva.

Some aspects of technique described are at variance with that in general use in many American clinics, but these modifications are the purpose of the book. The book does not read well, but this is undoubtedly due to translation and perhaps of little consequence in a volume which is primarily a manual of operative technique. The drawings are excellent and are the work of a physician artist.

The operative procedures described for carcinoma of the vulva would, by American or British standards, be less than adequate for the disease. The technique is the extirpation of the superficial inguinal glands only, and a vulvectomy which is considerably less than radical.

It is also hoped that the day is not too distant

when supravaginal hysterectomy no longer earns a place in a volume titled "Typical Gynecologic Operations."

Current Therapy—1960. By Howard F. Conn. 808 pages. Philadelphia, 1960, W. B. Saunders Company. \$12.00.

"Antepartum Care" through "The Menopause," in the section on "Obstetrics and Gynecology" in the above book is covered in a 60 page anthology listing 25 entities. The general tone and level of the section appears to be geared to the needs of the occasional practitioner of this specialty.

The discussion of "Apnea Neonatorum," although lamentably brief, makes several excellent points. We are reminded that apnea is often the result of cumulative insult and that nitrous oxide and oxygen analgesia has regularly caused delay in onset of neonatal respiration. The suggestion is made that the administration of oxygen to every parturient for 15 minutes prior to delivery is a good prophylactic measure.

The selections dealing with "Obstetrical Analgesia and Anesthesia," "Female Infertility," and "Bleeding in Late Pregnancy and Early Puerperium" were all well written and provide a good survey of the problems and therapy involved.

This reviewer was surprised to note an essay on "Normal Infant Feeding" included among the obstetrical and gynecologic papers.

The section on "Obstetrics and Gynecology" is worthwhile reading for all physicians, but the specialist may find the discussions to be on a rather elementary level.

Human Heredity. By Ashley Montagu. First edition. 397 pages, 31 tables, 45 figures. Cleveland, 1959, World Publishing Company. \$5.00.

The increase in atomic radiation and the attention focused upon its potential genetic effect has made it necessary for the average person to have some basic knowledge of heredity and genetics, and the mechanisms involved, in order to fully understand the problem. Ashley Montagu, a well-known anthropologist, has attempted to provide an approach which is sufficiently scientific to appeal to the scientist yet simple enough so that the lay person can come to an understanding of the subject. Unfortunately, a subject as complex as this with a scientific language of its own is not so easily reduced to the vernacular, so that a minimum of biological understanding and background is still necessary. To offset this basic scientific approach, the author has been able to emphasize the human interest aspect and bring out the points with references to common everyday facts which can be seen by anyone in his own surroundings.

The first part of the book deals with "The Meaning of Heredity" in which the mechanism of reproduction and Mendel's laws of inheritance are explained and discussed in relation to the effects of heredity versus environment both before and after birth on physical and mental traits of twins; heredity and crime, constitution, sex, and race. In regard to the unsolved argument of heredity versus environment, the author claims to present an unbiased, middle of the road policy, but a strong tendency to lean toward the nurture side of the fence and away from nature is present throughout the book.

In Part II, entitled "The Family Album," he discusses the heredity of common physical and functional traits such as hair and eye color, blood type, etc., and closes with a long list of inherited disorders in man which is as up-to-date and as complete as any list available today.

Of particular interest to physicians, and especially to the obstetrician, is the chapter, "The Effects of Environment Upon the Developing Human Being in the Womb," in which he discusses the relative roles of heredity versus environment and the effect of such factors as maternal age, maternal parity, maternal dysfunction, maternal sensitization, nutritional effects, infections, drugs, physical agents, emotional factors, and environment per se. This

purports to show that environment plays as much a role antepartum as heredity does in determining the health and condition of the fetus. A second chapter is "What Do We Do About Heredity," in which the problems of eugenics are discussed with no definite conclusion other than the choice should be on an individual basis rather than left to the state to decide.

In general, the book is pleasant and entertaining in addition to being enlightening for both the lay person and the physician, and it is recommended for anyone interested in a problem which is coming more and more before the public.

Fundamentals of Gynecology. By Samuel J. Behrman and John R. G. Gosling. 416 pages, 166 figures. New York, 1959, Oxford University Press, Inc. \$9.50.

The authors have accomplished their stated objectives of producing a concise, noncontroversial text on the fundamentals of gynecology oriented toward medical students and practitioners.

The book is well organized, easy to read, and outlined so that specific subject matter can be readily located. The chapter on pelvic anatomy is particularly well presented and the illustrations throughout the book are clear and expressive and they add to its comprehensive value.

Detail is minimized and controversial subjects are omitted in the interest of brevity and clarity; therefore, the reader interested in greater detail would need to refer either to the standard textbooks on gynecology or utilize the bibliographies provided at the end of most chapters.

In general, the authors have written a good introductory text in Fundamentals of Gynecology.

Oxygen Supply to the Human Fetus—A Symposium. Edited by James Walker and Alec C. Turnbull. 313 pages, 136 figures, 47 tables. Springfield, Ill., 1959, Charles C Thomas, Publisher. \$10.50.

This volume represents the formal and informal discussions of those who attended a conference concerned with maternal-fetal relationships. The subject matter covers a wide range. It is not limited to the oxygen molecule and it is not confined to the human species. Both clinician and basic scientist should enjoy perusing through this text.

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that each speaker presents material he has personally supervised and/or performed, there being little or no attempt to review the world literature. The points to be stressed are made with authority and clarity.

The discussions which follow each formal presentation are most appropriate, for they enable one to see how much and how little is known and accepted, how much and how little can be offered by present techniques, how accurate or inaccurate such techniques are, and how variable are the factors which must be considered in any study of human material.

This publication will serve well as a useful and fairly complete repository of present knowledge. There should be no feeling, however, that it represents the final word on oxygen supply to the human fetus.

A Textbook of Gynecology. By Laman A. Gray. 470 pages, 324 figures, 6 plates. Springfield, Ill., 1960, Charles C Thomas, Publisher. \$15.50.

The author states that the purpose of this book is to present in a brief and clear manner a new and modern summary of present-day gynecology. His teachings are sound and in accordance with the best practices in this country. However, careful reading reveals no startling innovations in form or content. Basic pathology is stressed as essential for diagnosis and treatment. Certain operative techniques are described briefly.

All illustrations are new. While most of the sketches and photomicrographs are satisfactory, the numerous tone drawings are poor except those illustrating operative procedures.

The section on pelvic inflammatory disease does not mention rupture of a tuboovarian abscess. Pelvic abscess is not clearly differentiated. Septic abortion and postabortal sepsis due to Clostridium welchii are not mentioned.

William K. Keller has contributed a chapter on "gynechiatry" (a word he has coined) which attempts to cover an extremely important subject in less than 6 pages.

A few references are listed at the end of each chapter. The book is a cumbersome quarto.

Gynecological Therapy. By Josef Novak. 258 pages, 18 figures, 4 tables. New York, 1960, McGraw-Hill Book Company, Inc. \$8.50.

Dr. Novak has prepared a concise book of the clinical course and therapy in the more common

gynecologic disorders. In addition, the author has included some points of therapy either unknown or long forgotten by the practitioners in our country today. The fields of hydrotherapy, thermotherapy, balneotherapy, pressure therapy, mechanotherapy, and light therapy and their applications in a host of disorders have been thoroughly reviewed.

The chapter on gynecologic tumors is presented in chart form and the chapter on innumerable drug preparations serves as a handy reference. More stress should be put on the consultation of a recognized specialist when necessary. Some methods of treatment suggested are controversial and used only in exceptional cases, if at all. In the chapter on radiotherapy the author suggests the use of radiation for menometrorrhagia, dysmenorrhea, and inflammatory genital disease. This is contrary to the prevalent feeling at this time.

Die Sexualhormontherapie in der Gynäkologie. By Friedrich Hoffmann. Third edition. 182 pages, 55 figures. Leipzig, 1959, Johann Ambrosius Barth. DM 11.

This scholarly monograph presents a staggeringly complete review of the literature on ovarian function and the hormonal regulation of menstruation, together with summaries of recommended methods of hormonal therapy. The text is forbiddingly turgid in style, including as it does a bewildering succession of names and statistics. The specific hormone preparations discussed are in many cases proprietary drugs available only in Europe, and this will reduce the value of the book for North American readers. Although the book is beautifully printed and bound, it presents its material in so indigestible a form that it can be recommended only for reference on specific points.

Lehrbuch der Gynäkologie fur Studium und Praxis. By Robert Schroeder. Fifth edition. 506 pages, 464 figures. Leipzig, 1959, Veb Georg Thieme. DM 48.

Professor Schroeder presents the fifth, extensively revised edition of his virtually classic textbook of gynecology, first published in 1922. It is a pleasure to be able to report that the new edition, which appears 14 years after the fourth edition, remains in every way worthy of its predecessor's high reputation.

Throughout the book, the most recent scientific advances have been systematically incor-

porated into the text. Clinical manifestations are constantly correlated with basic knowledge, and the thoroughness and clarity with which the author presents basic clinical diagnostic methods is commendable. When controversial subjects are discussed, the author meticulously presents the differing viewpoints without undue dogmatism. Although the therapeutic suggestions inevitably reflect the middle European rather than the North American point of view, most of the principles of treatment recommended by the author are in line with the best gynecologic practice throughout the world. The book is beautifully printed, and the illustrations are exceptionally well chosen and reproduced. Particularly commendable is the author's emphasis on basic pathologic anatomy, and the numerous photographs of microscopic and gross specimens are helpfully illustrative. The style is consistently straightforward and explicit, with a minimum of superfluous verbiage. This excellent textbook belongs in the library of all students of gynecology who possess a reading knowledge of German.

Combined Textbook of Obstetrics and Gynaecology. Edited by Dugald Baird. Sixth edition. 936 pages, 492 illustrations. Baltimore, 1957, Williams & Wilkins Company. \$15.00.

In the present edition of this well-known textbook the format as well as the text has been changed. Although much new material has been included the number of pages has been reduced to 936 from 1,411. The result is a compact volume which attempts to correlate more closely obstetrics and gynecology. Special consideration is given to preventive measures as an integral part of the subject.

The editor took the opportunity of praising 4 famous men who together wrote the first edition of the *Combined Textbooks* 34 years ago—Munro Kerr, Haig Ferguson, James Hendry, and James Young. Of the 2 still alive only James Young remains as a contributor to the sixth edition.

This book is highly recommended to American readers.

Books received for review

- Biochemistry of Human Genetics. By 29 participants in Ciba Foundation Symposium, G. E. W. Wolstenholme and C. M. O'Connor, editors for Ciba. 847 pages, 60 illustrations. Boston, 1959, Little, Brown & Company. \$9.50.
- Cancer of the Cervix—Diagnosis of Early Forms. By Ciba Foundation Study Group No. 3, G. E. W. Wolstenholme and Maeve O'Connor, editors. 114 pages, 27 figures. Boston, 1959, Little, Brown & Company. \$2.50.
- Childbirth Without Pain. By Pierre Vellay and others (translated from the French by Denise Lloyd). First edition. New York, 1960, E. P. Dutton & Company, Inc. \$3.95.
- Clinical Endocrinology. Edited by Edwin B. Astwood. First edition. 724 pages. New York, 1960, Grune & Stratton, Inc. \$18.75.
- Colposcopie. By Jules Bret and Fernand Coupez. 270 pages, 121 figures, 2 color plates. Paris, 1960, Masson et Cie. 45.00 NF.

- Complications of Pregnancy. By Staff of Mount Sinai Hospital, edited by Alan F. Guttmacher and Joseph J. Rovinsky. 619 pages, 47 figures, 36 tables. Baltimore, 1960, Williams & Wilkins Company. \$16.50.
- A Dictionary for Medical Secretaries. By Isabel Alice Stanton, 175 pages. Springfield, Ill., 1960, Charles C Thomas, Publisher. \$6.50.
- Edema—Mechanisms and Management. By John H. Moyer and Morton Fuchs. 833 pages. Philadelphia, 1960, W. B. Saunders Co. \$15.
- La Endometriosis. By Donato Gonzalez Marmol.Havana, 1959, Roger A. Queralt, Artes Graficas.
- Fermente—Hormone—Vitamine, Vol. 2, Hormone. By R. Ammon and W. Dirscherl. Third edition. 897 pages, 144 figures, 88 tables. Stuttgart, 1960, Georg Thieme Verlag and Intercontinental Medical Book Corp., New York City. DM 148. (\$35.25) or subscription price DM 125.80 (\$29.95).

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- From Fish to Philosopher—The Story of Our Internal Environment. By Homer W. Smith. Ciba edition, revised and enlarged, 304 pages. Summit, 1959. Issued by Ciba Pharmaceutical Products, Inc., with permission of Little, Brown & Company, Boston.
- Fundamentals of Clinical Hematology. By Byrd S. Leavell and Oscar A. Thorup, Jr. 503 pages, 71 figures, 20 tables. Philadelphia, 1960, W. B. Saunders Company. \$10.00.
- Gynäkologen Deutscher Sprache—Biographie und Bibliographie. By H. Kirchoff and R. Polacsek. Third edition. 630 pages. New York, 1960, Intercontinental Medical Book Corp. \$11.40.
- High Blood Pressure and Pregnancy. By Lance Townsend. 115 pages, 22 figures, 26 tables. New York, 1960, Melbourne University Press and Cambridge University Press. \$8.50.
- British Medical Bulletin—Antibiotics in Medicine. By L. P. Garrod, scientific editor. 88 pages, illustrated. London, 1960, Medical Department, British Council. \$3.25.
- De klinische Waarde van Methyl-Oestrenolon en Allyl-Oestrenol bij Menstruatie stoornissen en Bedreigde Zwangerschap. By Hermanus Willemsen. 88 pages, illustrated. Leiden, 1960, Batteljee & Terpstra.
- Lifespan of Animals (Colloquia on Ageing). By 27 contributors, G. E. W. Wolstenholme and M. O'Connor, editors. Vol. 5, 370 pages, 58 illustrations and cumulative index to vols. 1 to 5. Boston, 1959, Little, Brown & Company. \$9.50.

- Nine Month's Reading—A Medical Guide for Pregnant Women. By Robert E. Hall. 191 pages, illustrated. New York, 1960, Doubleday & Company, Inc. \$2.95.
- The Office Assistant in Medical Practice. By Portia M. Frederick and Carol Towner. Second edition. 407 pages, 76 figures. Philadelphia, 1960, W. B. Saunders Company. \$5.25.
- Protection in Diagnostic Radiology. By B. P. Sonnenblick. 346 pages, 52 tables, 93 figures. New Brunswick, N. J., 1959, Rutgers University Press. \$7.50.
- Recent Advances in Biological Psychiatry. Edited by Joseph Wortis. Vol. II, 417 pages. New York, 1960, Grune & Stratton, Inc. \$13.50.
- Sex Differentiation and Development. Edited by C. R. Austin. 198 pages. New York, 1960, Cambridge University Press. \$8.50.
- Significant Trends in Medical Research, Series 50. Edited by G. E. W. Wolstenholme, C. M. O'Connor, and Maeve O'Connor. 356 pages, 41 illustrations. Boston, 1959, Little, Brown & Company. \$9.50.
- Typical Gynecologic Operations. By Siegfried Tapfer (translated by L. M. Szamek). First English edition from second German edition. 81 pages, 168 figures. Philadelphia, 1960, J. B. Lippincott Company. \$9.00.
- Virus Virulence and Pathogenicity. Ciba Foundation Study Group No. 4, G. E. W. Wolstenholme and C. M. O'Connor, editors. 114 pages, 13 illustrations. Boston, 1960, Little, Brown & Company.

Selected abstracts

Acta obstetricia et gynecologica scandinavica

Vol. 37, Suppl. 1, 1958.

*Aren, Per: Legal Abortion in Sweden: Tentative Evaluation of Justification of Frequency During Last Decade, pp. 1-75.

Aren: On Legal Abortion in Sweden, pp. 1-75. Since the expansion of the Swedish Abortion Law in 1946, gynecologists are not infrequently requested to induce abortion on medicosocial

grounds. During the last decade the frequency of legal abortions has been fairly high, and in 1951 it reached a maximum of 57.4 per 1,000 living children born. The increase in frequency of legal abortion in Sweden has been disquieting, especially as no evidence has been produced that criminal abortion has become less common. Much suggests that the total number of abortions has not decreased, but increased. It has been suggested that since 1946 a new type of abortion clientele has developed, one consisting mainly of married women. Furthermore, the Abortion Law presupposes prognostication for

^{*}These articles have been abstracted.

which no methods are as yet available. The law legalized the induction of abortion if, in view of the living conditions and other circumstances, it may be assumed that the mother's physical or mental strength would be sincerely impaired by the arrival and care of the child. This new indication was called "foreseen weakness," and it placed a heavy burden on the shoulders of psychiatrists and gynecologists.

In an attempt to assess the justification of the frequency of legal abortion during the last decade in Sweden, the author made an analysis of data obtained from the Hospital records of 248 women who had had legal abortions induced and had become pregnant (389 pregnancies) again. About one fourth underwent a new legal abortion (one third had applied), while about two thirds gave birth in one occasion or more (remainder: extrauterine pregnancy, spontaneous or criminal abortion).

Interviews of 100 unselected women who had had a legal abortion prior to giving birth to a child revealed that none of the latter pregnancies had been accompanied or followed by any appreciable injury to their health or impairment of their working capacity. About one half of these 100 women were living under similar conditions as at the time of legal abortion. Fourteen women stated that they had desired to have a substitute for the child they had earlier not borne, and 20 stated that although the pregnancy was unwelcome, they could not bear the idea of going through a new abortion.

Of 197 women in whom pregnancy had not been interrupted although legal abortion had been granted, 2 had died and 33 had had miscarriages. The remaining 162 women gave birth. The child died during or within one week of delivery in 7 women (5 per cent). In 12 cases (7 per cent) the women had the child adopted. The remaining 143 (88 per cent) kept the child. The abortion had been granted in all these cases on psychiatric or sociopsychiatric grounds. In none of the cases did any serious complication occur during pregnancy or delivery. In 94 per cent the women were psychologically adjusted to the child. In 79 per cent of cases, mental health was as before or better. In the remaining 21 per cent mental health had become worse but the deterioration was usually insignificant, and in approximately half of the cases it was apparently due mainly to factors other than the arrival of the child. The subsequent course showed that it was justified to refrain from operation in 127 cases (89 per cent) but not in the remaining 15 (11 per cent). One woman who had schizophrenia both at the time of application and of the review could not be satisfactorily interviewed and was excluded in the analysis.

The author concluded that if legal abortion is to be regarded as a therapeutic measure, the observations set forth above suggest that a more restrictive attitude should be adopted in the evaluation of the grounds for legal abortion.

Robert E. L. Nesbitt, Ir.

British Medical Journal

Vol. 2, Nov. 14, 1959.

*Sinha, A. C.: Hydrops Tubae Profluens as a Presenting Symptom in Primary Carcinoma of the Fallopian Tube, p. 996.

*Jefferiss, Derek: A Case of Primary Carcinoma of the Fallopian Tube, p. 1002.

Sinha: Hydrops Tubae Profluens as Presenting Symptom in Primary Carcinoma of Fallopian Tube, p. 996.

The author presents 2 cases of primary carcinoma of the Fallopian tube, both of which were diagnosed preoperatively on the basis of an intermittent discharge of clear, watery fluid from the vagina which is termed "hydrops tubae profluens" or "hydrorrhea tubae intermittens." The author reviews the literature on primary Fallopian carcinoma and summarizes the statistics and shows that 61 per cent of all cases in the literature have presented this symptom and many people consider this symptom pathognomonic. He discusses etiology and symptomatology and histological patterns and gradings.

The author's 2 patients were treated with panhysterectomy and postoperative deep x-ray therapy and the first patient is alive today after 5 years, 3 months, while the second patient, who did not show any invasion of the muscularis and did not receive any deep x-ray treatment, is also well 13 months postoperatively.

Stuart O. Silverberg

Jefferiss: Primary Carcinoma of Fallopian Tube, p. 1002.

This is a case report of primary carcinoma of the Fallopian tube in a 72-year-old woman who presented with a chief complaint of vaginal bleeding. On examination, a pelvic mass was felt above the symphysis that disappeared following examination when the patient noted severe vaginal bleeding accompanied by a watery discharge. Laparotomy was performed on the basis of carcinoma of the corpus uteri. However, a primary lesion of the distal portion of the left tube was found. A total hysterectomy and bilateral salpingo-oophorectomy were carried out. Pathologic examination revealed a well-circumscribed, well-differentiated adenocarcinoma of the tube.

Stuart O. Silverberg

Nov. 28, 1959.

*Dimsdale, Helen: The Epileptic in Relation to Pregnancy, p. 1147.

Dimsdale: Epileptic in Relation to Pregnancy, p. 1147.

The absolution of many of the stigmas surrounding epilepsy and improved drugs for therapy have enabled many of these people to lead normal social lives and as a result the number of epileptics who present with pregnancies has significantly increased.

In regard to the effect of pregnancy on epilepsy, approximately one third of these patients note an increase in seizures during pregnancy. A great many patients go through without change and occasionally amelioration results, perhaps because of better therapy. The problem of gestational epilepsy is discussed in which cases the epilepsy develops primarily in a first or later pregnancy. It is postulated that fits appearing after a disturbance of consciousness at the time of delivery may have resulted from a vascular lesion of the temporal lobe secondary to the delivery.

Hydration, alkalosis, and reduction of serum electrolytes are changes which result in seizures in the epileptic and are also changes associated with the pregnant state. It is noted that rapid increase in weight usually precedes the appearance of more frequent epileptic seizures and therefore epileptic patients should be carefully watched for this symptom. The epileptic need not be discouraged from pregnancy; however, this complication should not be considered lightly.

Management of pregnancy with epilepsy consists of suitable anticonvulsant therapy, control of anemia, and prevention of excess fluid retention as in toxemia.

Stuart O. Silverberg

Dec. 5, 1959.

*Buckle, A. E. R.: Methotrexate in Treatment of Metastasizing Chorio-carcinoma—A Case Report, p. 1210. *Walker, Norman: The Case for Conservatism in Management of Foetal Distress, p. 1221.

Buckle: Methotrexate in Treatment of Metastasizing Chorio-carcinoma, p. 1210.

The author presents a case of metastasizing choriocarcinoma treated with methotrexate and 6-mercaptopurine as one of the first efforts in England to utilize these drugs for the treatment of this disease. This is the case of a 35-year-old woman who was found to have choriocarcinoma with metastasis $2\frac{1}{2}$ months post partum, following 3 episodes of postpartum bleeding, of which 2 were treated by dilatation and curettage.

Following the first course, some resolution of the pelvic tumor mass and vaginal metastasis was noted; however, new pulmonary lesions were seen. A second course of methotrexate combined with 6-mercaptopurine was given with almost complete regression of the vaginal metastasis and considerable diminution in the size of the abdominopelvic mass with a drop in urinary gonadotrophin titers to negative on two occasions. Seventy days after the start of therapy the patient began to deteriorate with an increase in both primary and secondary growths and an increase in urinary gonadotrophin. The patient developed a small bowel obstruction due to inflammatory adhesions and died 10 days postoperatively. Autopsy revealed complete involvement of the genital organs and numerous pulmonary metastases. The author makes a plea for collection of more cases and larger trial of this form of treatment.

Stuart O. Silverberg

Walker: Case for Conservatism in Management of Foetal Distress, p. 1221.

Fetal distress is a problem of deep concern to all obstetricians. However, there is considerable disagreement in the literature as to what really represents fetal distress and what its proper management is. The author has studied 700 cases of fetal distress, 350 of which formed the basis of a controlled study, being blindly selected for either conservative management or treatment by active intervention.

Analysis of the findings showed the meconium staining, regardless of degree, was associated with a threefold increase in perinatal mortality whereas alteration of fetal heart rate, with or without meconium staining, in no way altered the fetal outcome. The author concludes therefore that meconium staining of the liquor amnii

is the one definite sign of fetal distress, whereas the behavior of the fetal heart is of doubtful value in evaluating fetal distress. The prognosis of fetal distress was effectively the same whether treated by active intervention or conservatively. The majority of the fetal loss was associated with underlying obstetrical conditions which possibly contributed to the fetal distress, chiefly cephalopelvic disproportion, and the outcome was again unaffected by the type of management, being equally elevated in both groups. The author feels, therefore, that the danger of fetal distress depends upon the presence of underlying complications and that the onset of distress should be an indication to search for the cause rather than a demand for dramatic action. Stuart O. Silverberg

Dec. 19, 1959.

*Theobald, G. W.: Home on the Second Day: The Bradford Experiment, p. 1364.

Theobald: Home on the Second Day: The Bradford Experiment, p. 1364.

In 1951, in an attempt to reduce the high incidence of pre-eclampsia and eclampsia, the staff of the St. Luke's Maternity Hospital in Bradford evolved a pilot scheme for improved clinic care and increased utilization of antenatal hospitalization for control of progressive toxemia. Because of the limitations of bed space, it was necessary to reduce the number of lying-in beds to provide the additional antenatal beds. In order to achieve the reduction in lying-in beds they ultimately found the only solution to be early discharge of postpartum patients.

The results of the vigorous antepartum care program resulted in a reduction of perinatal mortality associated with hypertensives to 3.6 per cent with no deaths from eclampsia in the past 4 years.

As regards the early discharge program, the patients sent home within 48 hours were followed by their general practitioners and by domiciliary medicines. During the first year 741 (26 per cent) of all women delivered were thus followed. The remainder or 74 per cent were kept to the tenth day of the puerperium. Of the 741 mothers discharged within 48 hours, 3 were readmitted—2 because of secondary postpartum hemorrhage and one because of pyrexia. Fortyfour others required medical aid for reasons such as mild pyrexia, engorged breasts, subinvolution of uterus, headaches, etc. Four babies were admitted to the pediatric wards with the following diagnosis: subendocardial fibroelasto-

sis; staphylococcal ophthalmia neonatorum, physiological jaundice, and subdural hematoma; all recovered and went home. Fifty-four required medical attention for minor conditions. There were no puerperal complications directly attributable to early discharge.

In conclusion, they feel that the early discharge of patients has made it possible to improve antenatal care and prevent toxemia. It is not fraught with danger, could be economical, savors of common sense, and may indicate the future pattern of obstetrics. It will involve reorientation of obstetric and pediatric thought and the further development of home help service possibly on a local and part-time basis.

Stuart O. Silverberg

Vol. 1, Jan. 30, 1960.

*Pleydell, M. J.: Anencephaly and Other Congenital Abnormalities, p. 309.

Pleydell: Anencephaly and Other Congenital Abnormalities, p. 309.

An epidemiological study in Northamptonshire suggests that anencephalic births are related to density of population, since the incidence of anencephaly in urban districts is twice that of rural districts and its incidence in the industrial belt is three times that of the rest of the country. A second feature of anencephaly is its occurrence in groups in time and space.

Evaluating the cases of anencephaly since 1944 according to social class, season, population density, and grouping of births results in the conclusion that there is significant grouping of cases which can best be explained on the basis of infectious causation.

In a retrospective study of a small group of these cases the author suggests that the causative agent associated with congenital abnormalities may be Asian influenza. He stresses the need for further epidemiological inquiries in regard to congenital abnormalities.

Stuart O. Silverberg

Feb. 6, 1960.

*Appleby, S. P.: A Study of Premenstrual Tension in General Practice, p. 391.

Appleby: Study of Premenstrual Tension in General Practice, p. 391.

Earlier studies on the etiology and treatment of premenstrual tension are reviewed, and a study of 30 consecutive patients with premenstrual tension is reported. The patients were given 3 month trials with each of the following: a

diuretic, a tranquilizer, two types of oral progesterone, and a placebo. The drugs were given in a random order. At the end of each 3 month period the patient evaluated her symptoms on a questionnaire. The total trial therefore lasted 15 months. Over one half of the patients obtained complete relief or marked improvement with meprobamate, one third with chlorothiazide, and one fifth with progesterone derivatives. An interesting feature was that patients rarely responded well to more than one agent.

The author suggests that premenstrual tension is undoubtedly connected with some form of hormonal imbalance and water retention in many cases, but in addition, a marked functional element overshadows the somatic symptoms and he strongly suspects dual causation.

Stuart O. Silverberg

Feb. 13, 1960.

*Abbas, T. M. and Tovey, J. E.: Proteins of the Liquor Amnii, p. 476.

Abbas and Tovey: Proteins of the Liquor Amnii, p. 476.

This study presents an evaluation of the results obtained with paper electrophoresis of the protein pattern in the amniotic period, maternal serum, umbilical cord blood, and in vitro dialysates.

Samples of liquor amnii and venous blood were collected from 11 essentially normal patients in whom labor was surgically induced at 40 weeks plus 5 days. The amniotic fluid was withdrawn from the hindwater with a Drew Smythe catheter. In 7 additional cases maternal blood was provided to allow serum for in vitro dialysis against normal saline across their respective "fetal" membranes. The findings in the dialysates were then compared to those in the original amniotic fluid from the same patient.

In the analysis of protein functions, the pattern seen in the liquor amnii has the characteristics of a simple protein dialysate and can be duplicated closely by dialysing maternal serum across the corresponding fetal membranes, regardless of orientation of the membranes.

Evidence is also presented to suggest that the swallowed liquor amnii contributes to total nutrition and may well provide a source of gamma globulin and antibodies to the fetus.

No diagnostically significant changes were noted in toxemia, anencephaly, twins, hydramnios, or hydrops fetalis. Stuart O. Silverberg

Feb. 27, 1960.

*Jeffcoate, T. N. A.: Indications for Therapeutic Abortion, p. 581.

Jeffcoate: Indications for Therapeutic Abortion, p. 581.

The role of therapeutic abortion is still as much a problem to evaluate as it was 100 years ago despite changing indications. Since controlled observations are impracticable and the outcome for the patient if abortion had not been induced can never be known with certainty, any conclusions that may be drawn are rarely anything more than opinions. In this author's experience of 63 cases during the past 10 years, representing an incidence of approximately 1 in 1,000 cases, the indications changed significantly between the first 5 years and the second 5 years. Heart disease, in spite of recent advances in management, remained the most common indication. These patients were almost all multigravidas with histories of congestive failure in previous pregnancies or earlier in the aborted pregnancy. Pulmonary tuberculosis was the indication for 11 abortions. However, 10 of these cases were during the first 5 year period and this indication has almost disappeared with efficient antibiotic therapy. A new indication of recent years is pulmonary insufficiency resulting from diminution of vital capacity below 1,500 because of pneumonectomy or severe bilateral pulmonary disease or kyphoscoliosis. Other indications included chronic hypertension related to previous obstetrical complications; renal incompetence, present or past history of cancer, and psychiatric indications. Only one case based on obstetrical indications could be found, and this was based on uncontrollable hemorrhage from a placenta previa. Potential fetal abnormality as an indication is discussed and the conclusion reached that abortion purely on the basis of rubella, for example, is acceptable only by showing that the mother is so worried about the fetal prospect that her health is endangered. The indication then becomes maternal rather than fetal. In Rh incompatibility with previous stillbirths, the mother's health is endangered by the increased incidence of toxemia and abruptio placenta associated with hydrops.

It is stressed that in all cases the patients' individual attitudes, needs, and desires are the most important considerations in deciding upon a therapeutic abortion and must be kept uppermost in mind.

Another point brought out is that an induction of abortion nowadays really offers hope of improvement or cure of the patient's disease; it generally aims to do no more than prevent deterioration of the mother's condition, and is therefore more often prophylactic than therapeutic.

Stuart O. Silverberg

Vol. 1, April 30, 1960.

Mattingly, D. Mills, I. H., and Prunty, F. T. G.: Treatment of Simple Hirsutism Including the Hirsute Type of Stein-Leventhal Syndrome, p. 1298.

Cancer

Vol. 12, July-August, 1959.

Segaloff, A., Bowers, C. Y., Rongone, E. L., and Murison, P. J.: Hormonal Therapy in Cancer of the Breast, XIV. The Effect of 19-Nortestosterone Propionate Therapy on Clinical Course and Hormonal Excretion, p. 735.

Goldenberg, Ira S., and Hayes, Mark A.: Hormonal Therapy of Metastatic Female Breast Carcinoma, I. 9a-Bromo-11-Keto-Progesterone, p. 738.

Correspondence

Bibliographic omission

To the Editors:

"Attempts to Make an 'Artificial Uterus,'" an article by Taylor, Kolff, Sindeler, and Cahill, appeared on page 1295 of the June, 1959, issue of the Journal. There were neither biblio-footnotes within nor bibliography at the conclusion of the article.

It would appear therefore, according to ancient and modern tradition in medical writing, that, in the absence of previous references, the idea of an artificial uterus was original with the above-named authors.

Such is not the case, as is proved by the true bibliography of the artificial uterus which follows:

 Greenberg, E. M.: The Artificial Uterus, Scientific Exhibits Section, Convention, Medical Society of State of New York, Buffalo, New York, May 4, 1951.
 Greenberg, E. M.: Removable Foam Rubber

 Greenberg, E. M.: Removable Foam Rubber Obstetric Forceps Mittens and a Plan for an Artificial Uterus, Scientific Exhibits Section, Medical Society of State of New York, New York City, May 13, 1952.

 Greenberg, E. M.: The Artificial Uterus and the Passage of Radioactive Sodium Through Hemochorial Mammalian Placenta Extra Utero, Bull. New York Acad. Med. (Second Series) 30: 713, 1954.

 Greenberg, E. M.: The Artificial Uterus, American Society for Artificial Internal Organs, Hotel Chelsea, Atlantic City, New Jersey, June 5, 1955. (Introduced by W. J. Kolff, Chairman of the session.)

 Greenberg, E. M.: The Artificial Uterus, International Record of Medicine and General Practice Clinics, vol. 169, No. 5, May, 1956.

The artificial uterus as a project of Dr. Emanuel M. Greenberg was discussed by Stacy Jones, *New York Times* writer, in *Medical Economics*, Feb. 3, 1958.

In addition, articles on the artificial uterus have been deposited and are on file at the Boston Medical Library, The John Crerar Library of Chicago, the Library of the College of Physicians of Philadelphia, the Library of the New York Academy of Medicine, and the Army Medical Library, Washington, D. C. Requests for further information on the artificial uterus are forwarded to me from time to time from these libraries.

I also hold a patent on the artificial uterus, which was granted without the citation of previous references.

Aside from its being a breach of scientific ethics, this serious bibliographic omission undoubtedly has led and will lead the great majority of the general readership to entertain a false impression.

Bibliography in nondefinitive papers is often understandably incomplete, but this is not so serious as *no* bibliography at all in the face of the actual proved knowledge of the who, when, and where of the prior art.

It is interesting to note that one of the authors of "the article without a bibliography" presided as chairman and introduced the undersigned as the speaker on the artificial uterus, at an earlier presentation several years ago at a meeting of the American Society of Artificial Internal Organs (see Reference 4, above).

Emanuel M. Greenberg, M.D. 1141 Park Avenue New York 28, New York

May 11, 1960

Reply by Dr. Taylor

To the Editors:

The expression, "artificial uterus," is, of course, not an original one with the undersigned; and any interpretation that the authors referred to in Dr. Greenberg's letter claim originality for it is to be deplored. The authors have not and do not now claim such originality. On the other hand, the sense in which Dr.

Greenberg has used the expression, "artificial uterus," is quite different from the sense in which it is used in the paper referred to.

We are aware of Dr. Greenberg's work, have read his papers, and have heard his presentation; and it was our collective opinion that his work had no bearing on our own; hence, no reference was made to the discussion and publications to which he refers.

Howard P. Taylor, M.D.

2020 East 93rd Street Cleveland 6, Ohio June 10, 1960

Rupture of gravid uterus

To the Editors:

I should like to comment on the paper of Coralie W. Rendle-Short, which appears on pages 1114-1120 of the June, 1960, issue of the JOURNAL. This article pertains to the high incidence of rupture of the gravid uterus in Uganda, East Africa.

It is of interest that Narroll, Narroll, and

Howard, in reviewing the mores of delivery in primatives, found that the Bantu usually assumes an "all-fours" position for the second stage of labor. I do not recall what if anything was mentioned concerning the position that the Nilotic tribe usually assumes.

At any rate, Rendle-Short is at a loss to account for the incidence of rupture of the gravid uterus. May it not be that the unphysiologic positioning of these primatives may lead to improper stresses, mechanically speaking, causing a majority of tears to be anterior? In Table IV, anterior tears are 36 and those involving the bladder 10, whereas posterior tears are 9 in number.

It would be interesting for Rendle-Short to communicate to the Bantu women that they may be spared rupture of the uterus if they would change to a sitting or squatting position for delivery, as a goodly majority of other African Natives use.

Forrest H. Howard, M.D.

13051 Belfast Drive Garden Grove, California

Items

Two-day infertility symposium in New York

Sponsored jointly by the Margaret Sanger Research Bureau and the Department of Obstetrics and Gynecology of The New York Hospital-Cornell University Medical College, a 2 day Symposium on Infertility will be held in New York City, Oct. 13 and 14, 1960.

Operative clinics on infertility problems at The New York Hospital on Thursday, October 13, will be followed by round-table discussions, lectures, and demonstrations continuing on Friday, October 14, at the Margaret Sanger Research Bureau.

Attendance will be limited to 40 physicians. For further information and registration, write to Aquiles J. Sobrero, M.D., Assistant Director, Margaret Sanger Research Bureau, 17 West 16 Street, New York 11, New York.

Canadian Society for the Study of Fertility

The Sixth Annual Meeting of the Canadian Society for the Study of Fertility will take place at the Royal York Hotel, Toronto, Ontario, on Oct. 21 and 22, 1960.

Further information may be obtained by writing to the Secretary, Dr. George H. Arronet, Infertility Centre, Royal Victoria Hospital, Montreal 2, Quebec.

Formation of The Teratology Society

For several years scientists interested in basic problems of congenital malformations have held informal conferences. Anatomists, biochemists, embryologists, geneticists, obstetricians, pathologists, pediatricians, plastic surgeons, and others attended these conferences. With the increasing interest in this area, it was felt that there was a need for a Society to hold regular meetings in which investigations concerned with etiology and morphogenesis of congenital malformations could be presented and discussed.

Following the fourth teratology conference, "The Teratology Society" was formed with the following officers: president, Josef Warkany, M.D., Cincinnati, Ohio; president-elect, James G. Wilson, Ph.D., Gainesville, Florida; secretary-treasurer, Marjorie M. Nelson, Ph.D., San Francisco, California; recorder, Sidney Q. Cohlan, M.D., New York, New York.

Inquiries about The Teratology Society should be directed to Dr. Marjorie M. Nelson, Department of Anatomy, School of Medicine, University of California, San Francisco 22, California.

American Board of Obstetrics and Gynecology

The next scheduled examination (Part I), written, will be held in various cities of the United States, Canada, and military centers outside the Continental United States, on Friday, Jan. 13, 1961.

Candidates submitting applications in 1960 for the 1961 examinations are not required to submit case reports as previously required to complete the Part I Examinations of this Board. In lieu of this requirement, new candidates are required to keep in their files a duplicate list of hospital admissions as submitted with their application, for submittal at the annual meeting in Chicago should they become eligible to take the Part II (oral) Examinations.

Reopened candidates will be required to submit case reports for review 30 days after notification of eligibility. Scheduled Part I and candidates resubmitting case reports are required to submit case reports prior to August 1 each year.

Current Bulletins may be obtained by writing to the secretary.

Robert L. Faulkner, M.D. Executive Secretary and Treasurer 2105 Adelbert Road Cleveland 6, Ohio

Sessions devoted to gynecology and obstetrics at the Clinical Congress of the American College of Surgeons, San Francisco, Oct. 10-14, 1960

Wednesday, October 12 1:30-5:00 P.M.

- Forum on Gynecological and Obstetrical Research, Chairmen, Milton L. McCall, M.D., F.A.C.S., Pittsburgh, and Somers H. Sturgis, M.D., F.A.C.S., Boston.
- Interruption of Uterine Blood Flow: A New Technique for the Production of Congenital Malformations; Comparison of the Eighth, Ninth, and Tenth Days of Gestation, John B. Franklin, M.D., and Robert L. Brent, M.D., Philadelphia
- A Transistorized Fetal Heart Monitor, Edward H. Hon, M.D., New Haven
- Placental Homotransplantation Using the Millipore Chamber in the Rat, Ta-Jung Lin, M.D., Cleveland
- Effects of Maternally Administered Drugs on the Fetus in Utero, B. T. Jackson, M.D., G. J. Piasecki, B.S., and R. H. Egdahl, M.D., Richmond
- Host-Homograft Interactions Following Leukocytic Transfusion During Pregnancy, Richard H. Andresen, M.D., F.A.C.S., G. M. Hass, M.D., D. A. Madden, B.A., and S. Papadopoulos, Ph.B., Chicago

- The Role of the Mind in the Genesis of Toxemia of Pregnancy, C. A. Douglas Ringrose, M.D., Edmonton
- Germfree Guinea Pig Delivery by Hysterectomy, Jerome J. Landy, M.D., Theodore G. Yerasimides, D.V.M., James H. Growdon, M.D., F.A.C.S., and Sydney C. Bausor, Ph.D., Little Rock
- Intrauterine Fetal Hypophysectomy in Primates—A Technique, Donald L. Hutchinson, M.D., William H. Hindle, M.D., and J. L. Westover, M.D., Los Angeles
- A Technique for Reconstruction of Fallopian Tube: A Preliminary Report, A. G. Charles, M.D., J. E. Labes, M.D., M. R. Cohen, M.D., and W. C. Shoemaker, M.D., Chicago
- The Role of the Uterine Isthmus in Cervical Incompetence, Edward C. Mann, M.D., New York
- Pelvic Perfusion. I. The Feasibility of Isolation of the Vascular Compartment of the Canine Pelvis, George R. Prout, Jr., M.D., Norman Kenyon, M.D., W. Glen Moss, Ph.D., and Daniel S. Martin, M.D., Miami
- Thrombectomy for Acute Ilio-Femoral Venous Thrombosis, J. Alex Haller, Jr., M.D., Louisville







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Page 76

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References: 1. Angelucci, H. M.: Am. J. Obst. & Gynec. 50:336, 1945. 2. Hensel, H. A.: Postgrad. Med. 8:293, 1950. 3. Cortese, J. T.: Clin. Med. 2:45, 1955. 4. Dill, L. V., and Martin, S. S.: M. Ann. District of Columbia 17:389, 1948. 5. Horoschak, A., and Horoschak, S.: J. M. Soc. New Jersey 43:92, 1946.

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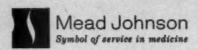
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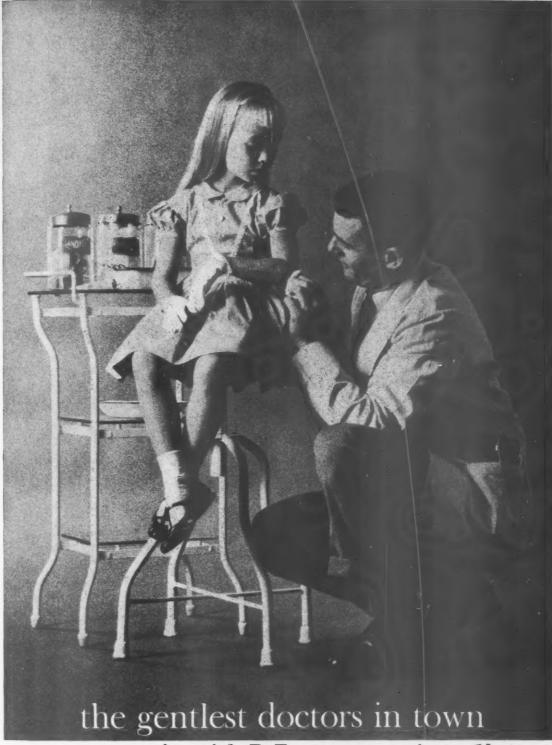


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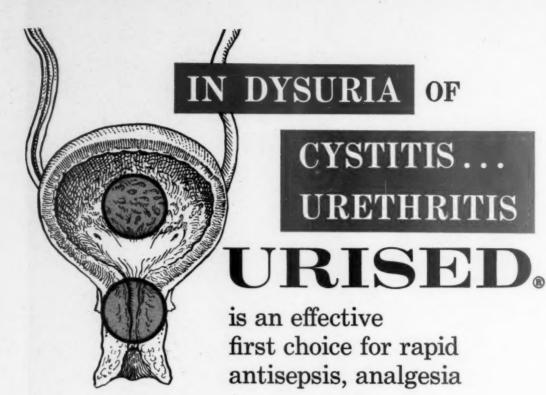
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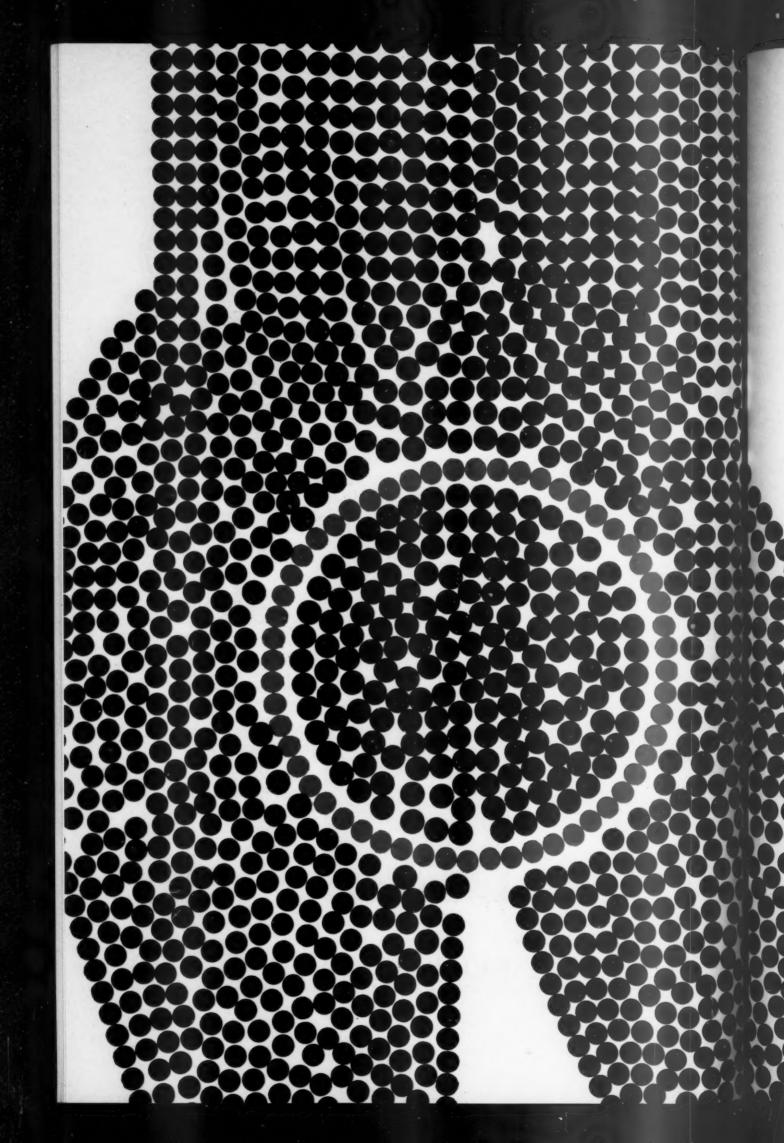


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85% SUCCESS: 1-2 TRIBURON CHLORIDE—THE CLINICALLY PROVEN MICROBICIDE—PROVIDES RAPID SYMPTOMATIC RELIEF AS WELL AS MICROBICIDAL CONTROL OF TRICHOMONAL, MONILIAL AND NONSPECIFIC VAGINITIS. IN ONE STUDY, DISCHARGE, ITCHING AND BURNING DISAPPEARED IN 67 OF 73 WOMEN AFTER ONLY 3 OR 4 APPLICATIONS; AFTER TWO WEEKS, CULTURES WERE NEGATIVE IN 61 PATIENTS. SIMILAR RESULTS WERE NOTED IN ANOTHER SERIES OF 55 WOMEN.2

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INDICATIONS: TRIB VAGINAL SUPPOSITORIES AND TRIBURON VAGINAL CREAM FOR VULVITIS AND VAGINITIS DUE TO TRICHOMONAS VAGINALIS, CANDIDA ALBICANS, NEMOPHILUS VAGINALIS AS WELL AS MIXED INFECTIONS, AFTER CAUTERIZATION, CONIZATION AND IRRADIATION; FOR SURGICAL AND POSTPARTUM TREATMENT. THERAPY MAY BE CONTINUED DURING PREGNANCY AND MENSTRUATION.

SUPPLIED: TRIB VAGINAL SUPPOSITORIES—BOXES OF 24, WITH REUSABLE APPLICATOR. TRIBURON VAGINAL CREAM—3-OUNCE TUBES WITH 18 DISPOSABLE APPLICATORS, CONSULT LITERATURE FOR DOSAGE REQUIREMENTS, AVAILABLE ON REQUEST, BEFORE PRESCRIBING.

REFERENCES: 1. N. MULLA AND J. J. McDONOUGH, ANN. NEW YORK AGAD. SC., 82:(ART. 1), 182, 1959. 2. L. E. SAVEL, D. B. GERSHENFELD, J. FINKEL AND P. DRUCKER, 1810., P. 186.



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decisive microbicidal therapy in a delicate matter not an antibiotic • not a nitrofuran

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as hormones alone often don't do



Fast-acting Milprem directly relieves both emotional dread and estrogen deficiency

Dosage: One Milprem tablet t.i.d. in 21-day courses with one-week rest periods; during the rest periods, Miltown alone can sustain the patient.

Composition: Miltown (meprobamate) + conjugated estrogens (equine).

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Literature and samples on request.

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Many physicians find that estrogen therapy is not enough for the woman who is also filled with anxiety by her menopause. Her emotional dread may make her so miserable that it becomes a real clinical problem.

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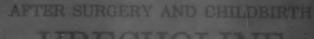
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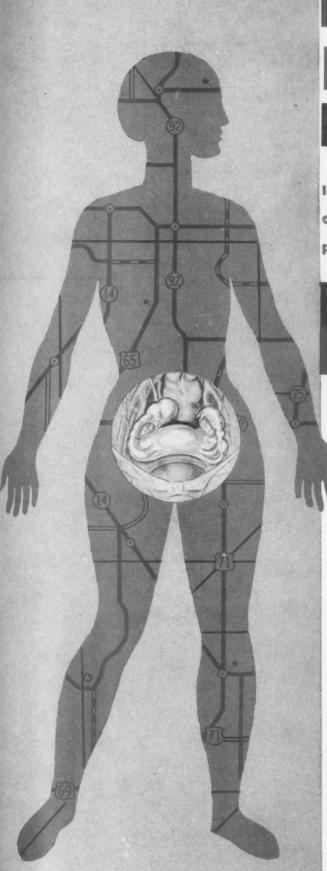
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REFERENCES: 1. Campbell, M. F.: Principles of Urology, Philadelphia, W. B. Saunders Co., 1957. 2. Colby, F. H.: Essential Urology, Baltimore, The Williams & Wilkins Co., 1953.

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"Of the group (15%) which did not respond to treatment, most had advanced pelvic masses which also had failed to respond to other conventional therapy used previously."

1. Reich, W. J., and Nechtow, M. J.: Am. Pract. & Digest Treat. 11:45, 1960. 2. Reich, W. J., and Nechtow, M. J.: Scientific Exhibit, Chicago Med. Soc. (March) 1960.

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references: (1) Voulgaris, D. M.: Dysmenorrhea - Treatment with Isoxsuprine, Obstetrics and Gynecology, to be published. (2) Busky, A.H., to be published.





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BONINE is an antiemetic which provides rapid and prolonged protection against nausea and vomiting due to a variety of causes, A single dose of BONINE is usually effective for 24 hours. Thus, BONINE can be taken at bedtime to help prevent "next morning" sickness.

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ADMINISTRATION AND DOSAGE: For control of nausea and vomiting of pregnancy, a daily dose of 25 to 50 mg. is usually effective. For dosage schedules in other indications, see package insert.

SIDE EFFECTS: Not a phenothiazine, the side effects reported in association with Bonine have been mild and/or transient and consist of occasional drowsiness, dryness of the mouth, and blurred vision. Drowsiness is seen less frequently with BONINE in therapeutic dosages than with most other effective antiemetics.

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The reason is usually tension.1,2,3 Now-Appetrol has been formulated to help you solve this problem.

Appetrol provides dextro-amphetamine to curb your patient's appetite. Even more important, it provides meprobamate to control compulsive overeating, to ease the frustration of the dietary regimen-and to minimize the jittery effects of amphetamine.

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Available: Bottles of 50 pink, scored tablets.

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References: 1. Freed, S. C.: Psychic factors in the development and treatment of obesity, J.A.M.A. 133:369, Feb. 8, 1947. 2. Kotkov, B.: Group psychotherapy with the obese. Paper read before The Academy of Psychosomatic Medicine, Oct. 1958. 3. Plotz, M.: Modern management of obesity—the "social diet." J.A.M.A. 170:1513, July 25, 1950

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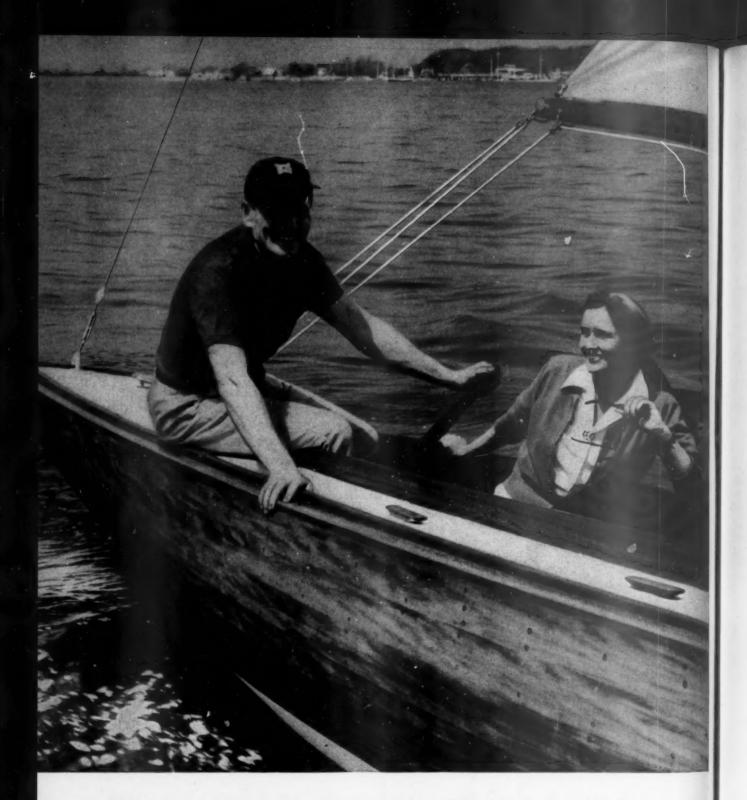
Bile salts — choleretic for treatment of biliary stasis; hydrotropic for soft, well-formed stools.

Stimulaxant — to improve smooth muscle tone, restore regularity.

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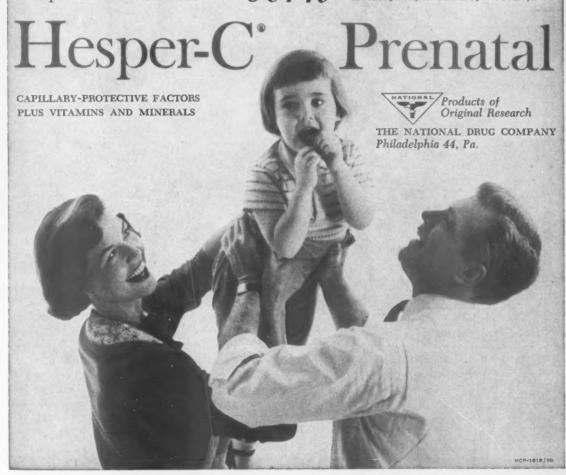
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1. Greenblatt, R. B.: Obst. & Gynec. 2:530, 1953, 2. Javert, C.: Obst. & Gynec. 3:420, 1954.



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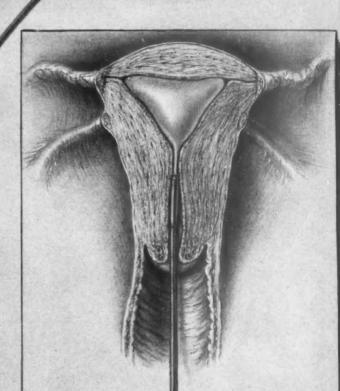


Illustration shows neck of balloon in isthmus and on injection, how the balloon distends first and fills the uterine cavity.

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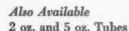
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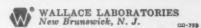
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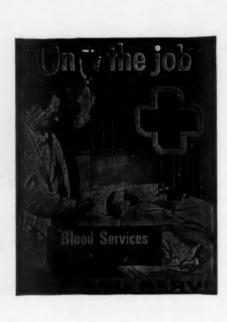
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-Natenshon, A. L.: Dis. Nerv. System 17:392 (Dec.) 1956.

"A double blind study of the mood elevating properties of Ritalin® in 112 patients showed statistically significant effect.... This drug offers great help in patients in whom elevation of the mood is desirable."

-Landman, M. E., Preisig, R., and Perlman, M.: J. M. Soc. New Jersey 55:55 (Feb.) 1958.

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> Pennington, V. M.: Mississippi Doctor 35:57 (Aug.) 1957.

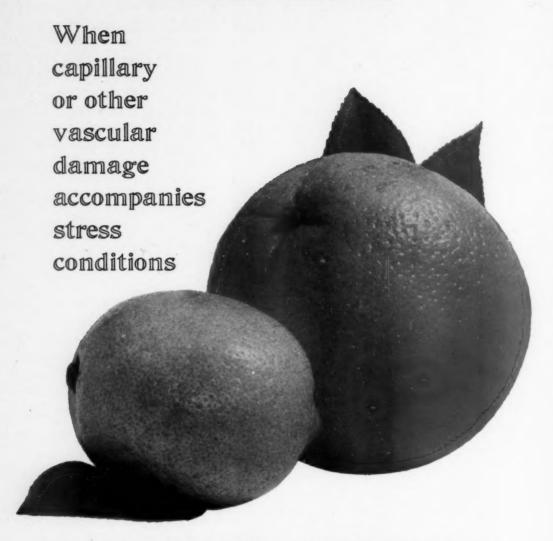
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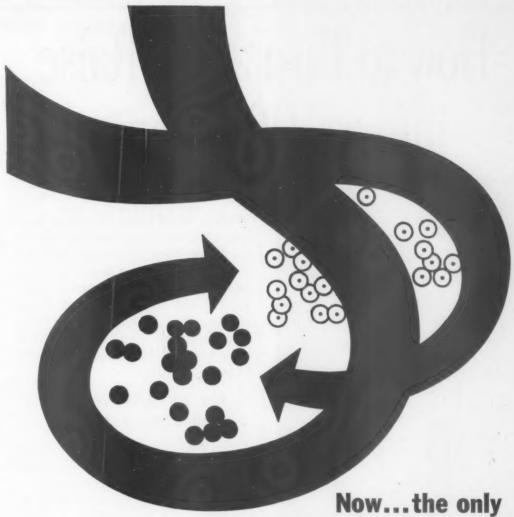




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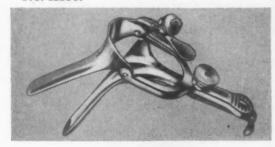
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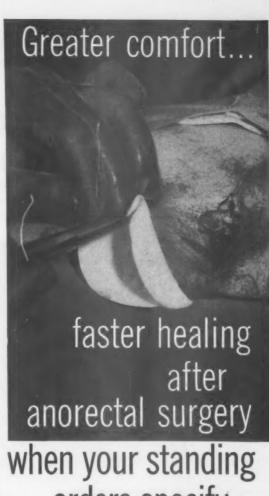


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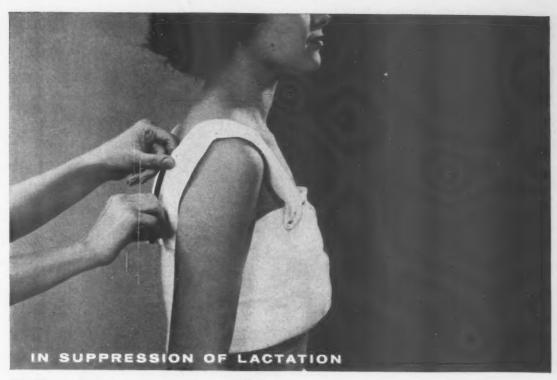
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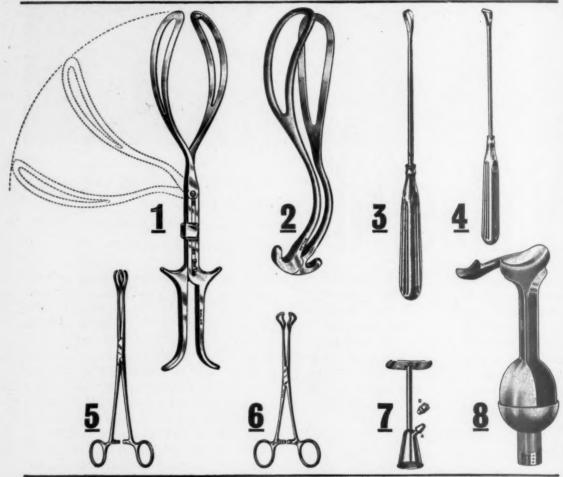
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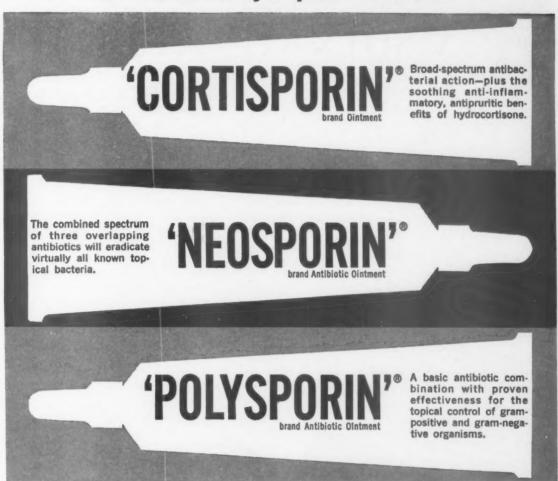
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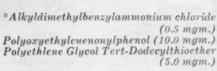
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Wizenberg, M. J., et al.: Am. J. Obst. & Gynec. 78: 405 (Aug.) 1959.

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